Valid double-dipping for fMRI cluster analysis via permutation-based selective inference

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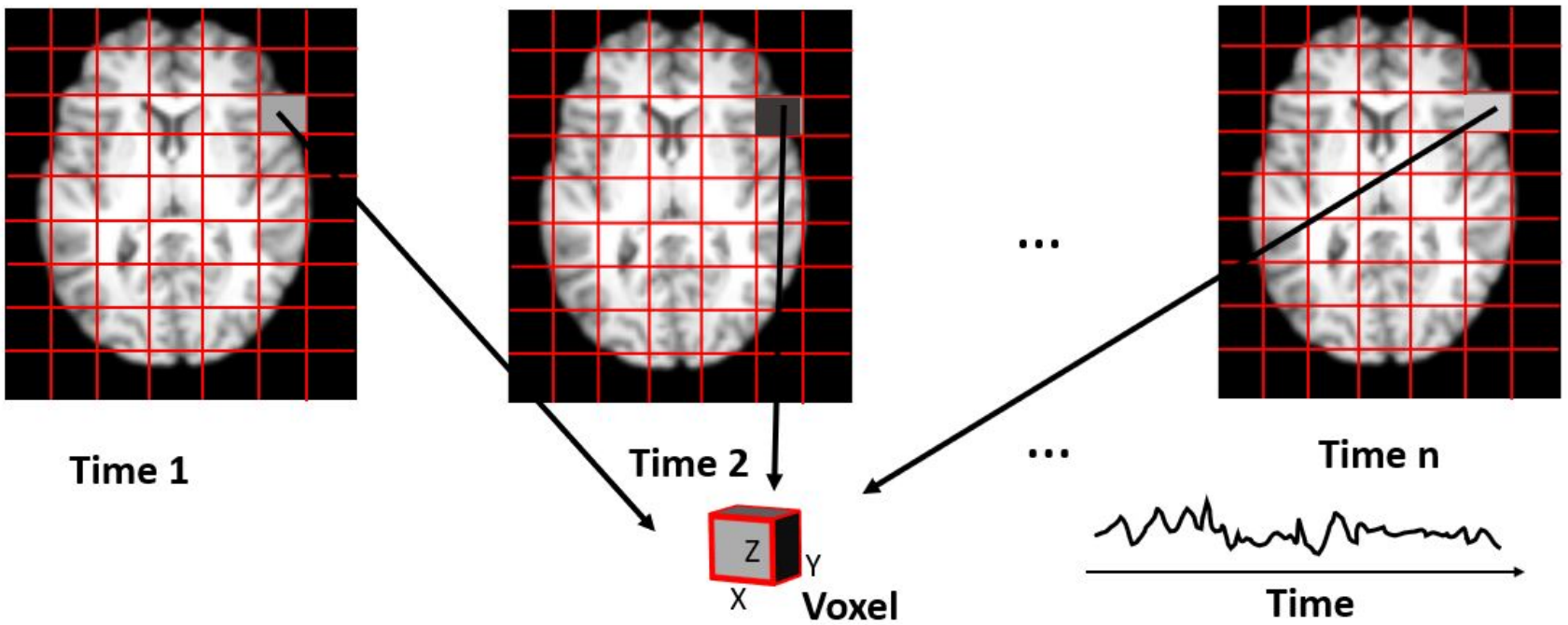
Functional Magnetic Resonance Imaging (fMRI) data

fMRI is the most used technology to study human cognition's neural underpinnings. The brain activation is measured as changes in blood flow (BOLD) under a sequence of **stimuli**.



Functional Magnetic Resonance Imaging (fMRI) data

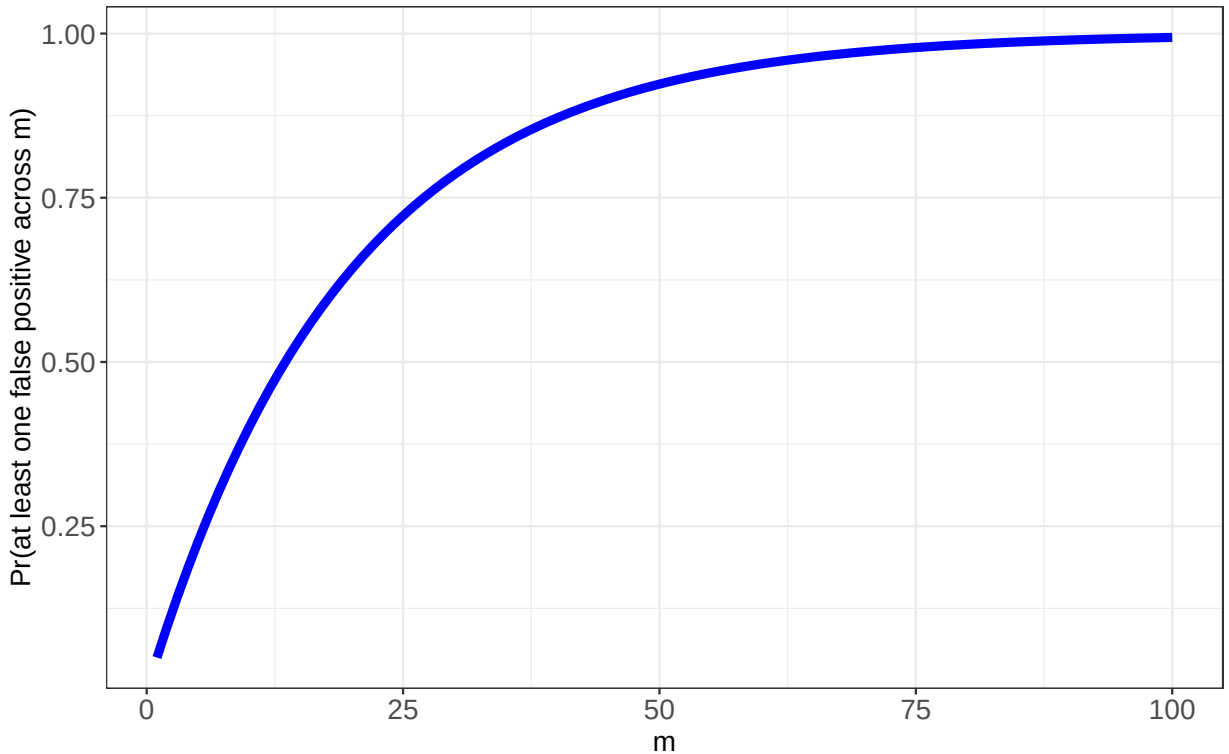
- **Response**: Brain activity measured for each **voxel** → about $200,000$ response activation to test.
- **Question**: Which regions respond differently to different **stimuli**? → is the region active?

So, We have a **test statistic**:

- for each voxel →
  H_v : voxel v is not active;
- for each set of voxels →
  H_S : the set of voxel S is not active .

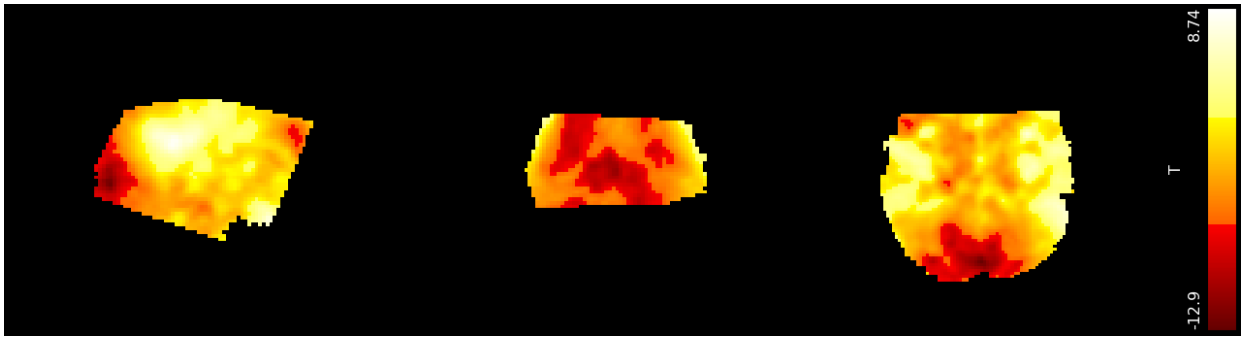
In a nutshell:

- When we test a single null hypothesis $H_0 \rightarrow$ the probability to reject H_0 when is true equals α (e.g., 0.05).
- If we test $m > 1$ null hypothesis, the probability to reject at least one hypothesis across m hypothesis equals $1 - (1 - \alpha)^m$

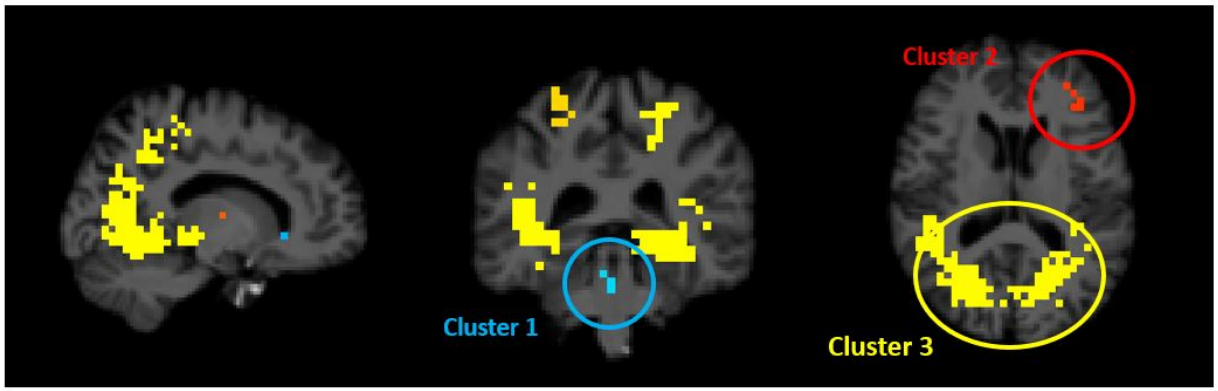


Multiple Testing problem

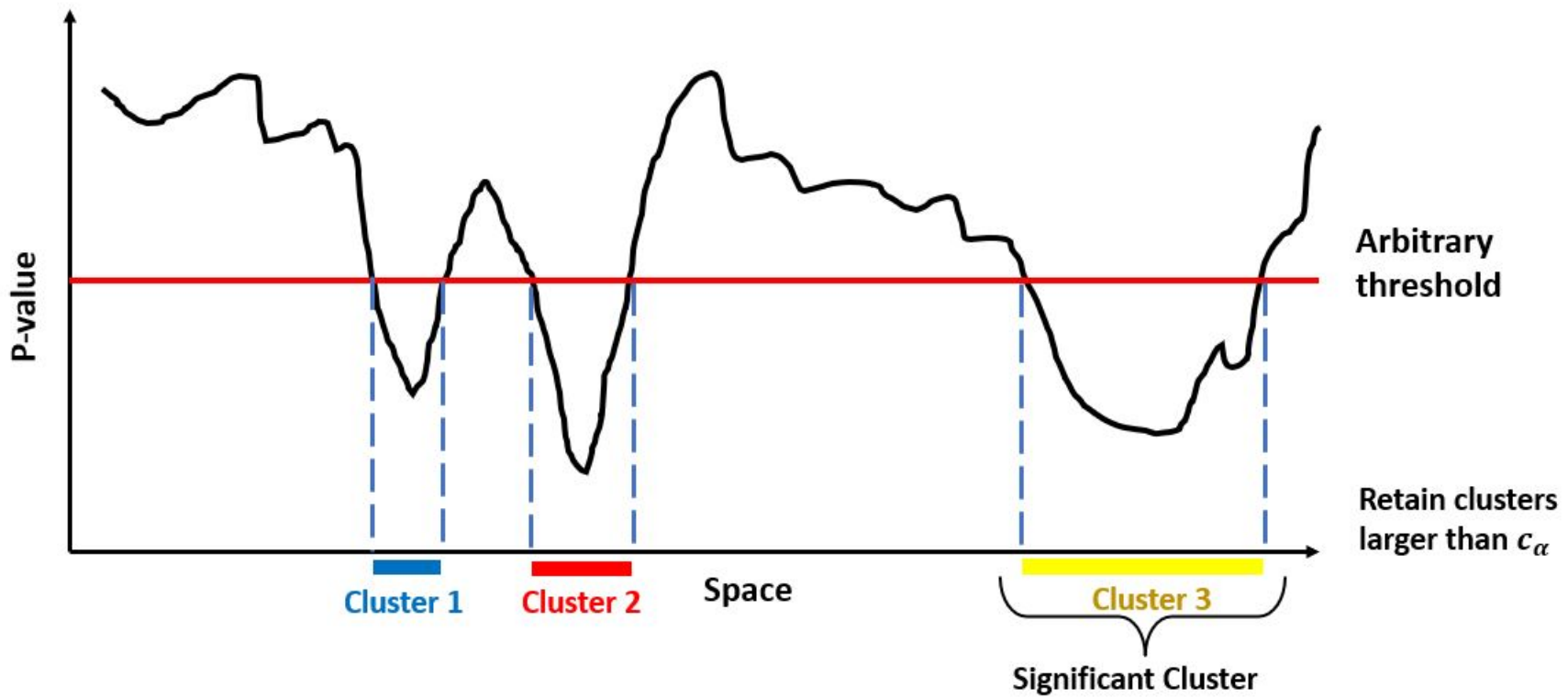
If we want to infer at voxel level $\rightarrow$ 200,000 statistical tests $\rightarrow$ $\alpha = 0.05/200,000$ (i.e., Bonferroni correction) $\rightarrow$ very low power to detect activation.



So, we can infer at level of set of voxels $\rightarrow$ 3 statistical tests $\rightarrow$ $\alpha = 0.05/3$ (i.e., Bonferroni correction) $\rightarrow$ we gain power.



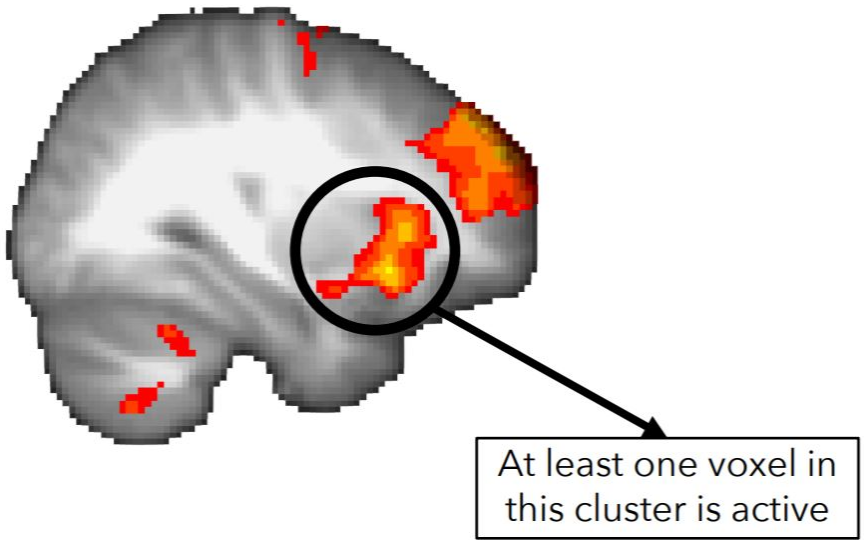
In fMRI data analysis, the most widely used method for locating brain activity is **cluster-extent based thresholding** [1].



[1] Woo, C. et al. (2014).

Problems:

- If we reject the null hypothesis we can only say:



Spatial Specificity paradox [2] →
The larger the cluster, the weaker the finding!

[2] Woo, C. et al. (2014).

- Inferring inside data-driven clusters leads to biased results!

  →

  Double-dipping

Solution:

- **Selective inference** approach: you can make post-hoc selection and follow-up inference (i.e., double-dipping);
- **Permutation-based** approach: account for the unknown dependence structure of voxels

Permutation-based All-Resolution Inference (**pARI**) → computes the lower bounds for the number of true active voxels inside each clusters (after seeing the data, changing the cluster-wise threshold, etc.).

Let consider B collection of m voxel activation to test.

- **Hypothesis**: $H_1, \ldots, H_m$;
- **True Discoveries**: $TD \subset \{1, \ldots, m\}$;
- **Cluster**: $S \subset \{1, \ldots, m\}$ selected hypothesis;
- **True Discoveries in S**: $|TD \cap S| \subset \{1, \ldots, m\}$.

We want to infer on $TD(S) = |TD \cap S|$ $\rightarrow$ compute the lower bound $\bar{TD}(S)$ $\rightarrow$ we can say "in S at least $\bar{TD}(S)$ are truly active".

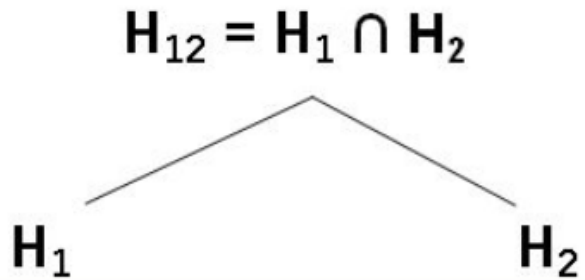
Two ingredients:

- **Closed testing procedure** for controlling the familywise error rate[3]:

$$\Pr(TD(S) \geq \bar{TD}(S) \text{ for each } S \in B) \geq 1 - \alpha$$

- **Local test** used in the closed testing procedure → permutation-based tests.

Closed testing rejects any H_i, if all possible intersection hypotheses involving H_i are rejected by using valid local level α tests.



Reject H_1 at level 0.05 if H_{12} is also rejected at level 0.05.

[3] Marcus, E. et al. (1976).

```
install.packages("pARI")
library(pARI)
```

- fMRI framework:

```
pARIbrain(copes, thr, mask, alpha, ...)
```

- General framework:

```
pARI(data, ix, alpha, test.type, ...)
```

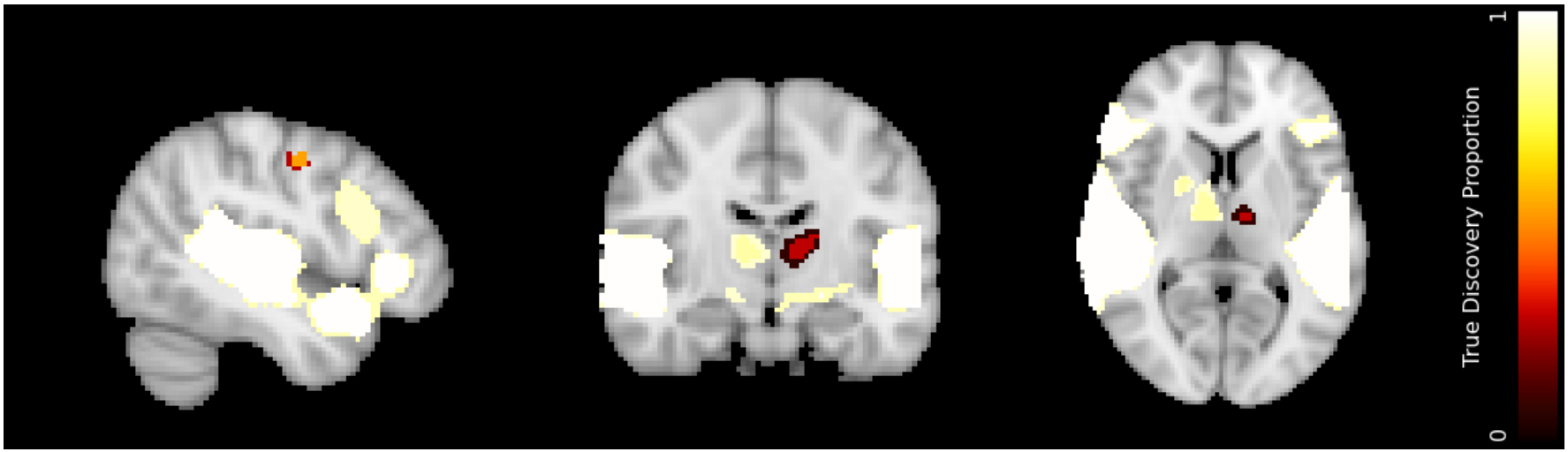
where `ix` is the **set** S of interest (i.e., vector of hypotheses indices).

We analyzed the **Auditory data** collected by Pernet et al. (2015), i.e, people listening vocal and non-vocal sounds.

Group analysis on 140 subjects of the Vocal > Non-vocal **contrast** by the one sample t-test flipping the sign of 140 voxel-wise contrasts maps.

Cluster S	**Threshold** t	**Size** $\lvert S\rvert$	**% active** $\bar{TD}(S)$ Perm. Simes	Param. Simes	**P-Values** p_{FWER}
Right STG/PT HG/IFG/T	3.2	11683	92.36%	84.98%	< 0.0001
Right STG/PT HG/IFG/T	4	8875	99.54%	98.5%	–
Right IFG	4	422	91.47%	83.18%	–
Right T	4	292	85.96%	64.04%	–
Right T	4	15	13.33%	0%	–

fMRI data



The **permutation-based ARI**:

- **flexible**, **mild** and **post-hoc** → You can choose the features set as many time as you want!
- resolves the **spatial specificity paradox** of cluster fMRI data analysis;
- accounts for the **dependence** structure of the data;
- makes **no assumptions** on the null distribution of the p-values → only **exchangeability**;
- the **power** does not depend on the number of features sets tested.