Centre for Molecular Medicine and Therapeutics



Multiple Testing

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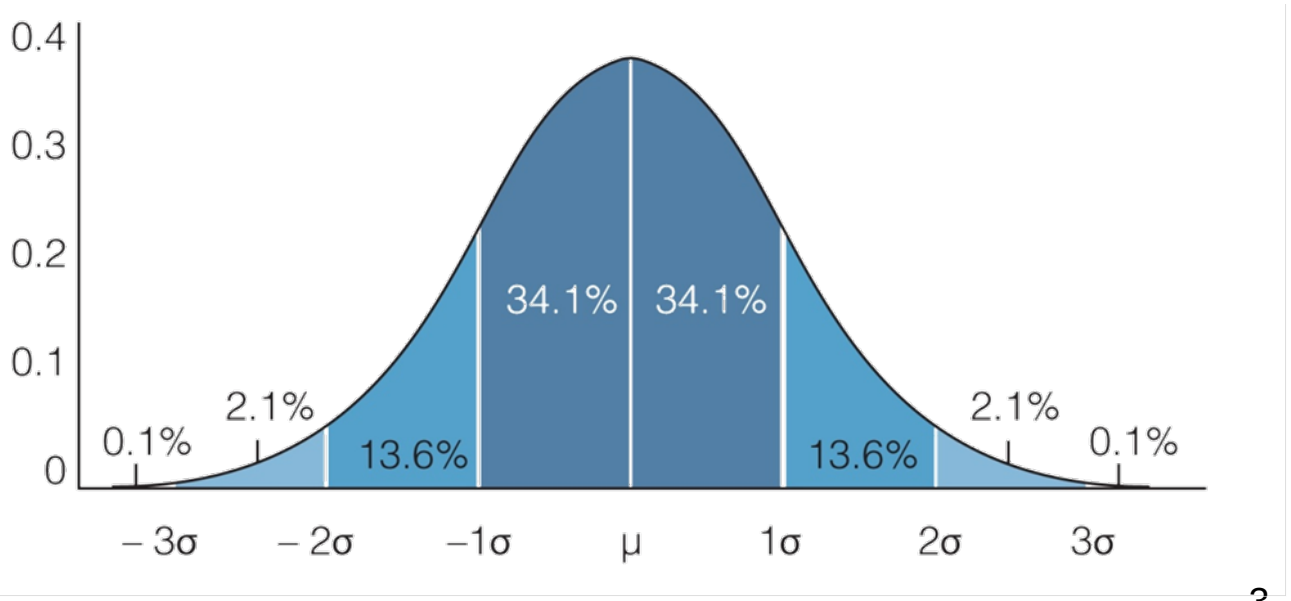
Outline

- Single Hypothesis Testing
- Multiple Hypothesis Testing
- Bonferroni Correction
- Step-up Procedure
- False Discovery Rate Correction
- Max-t Permutation Test
- Recent Topics
- Neuroimaging Applications

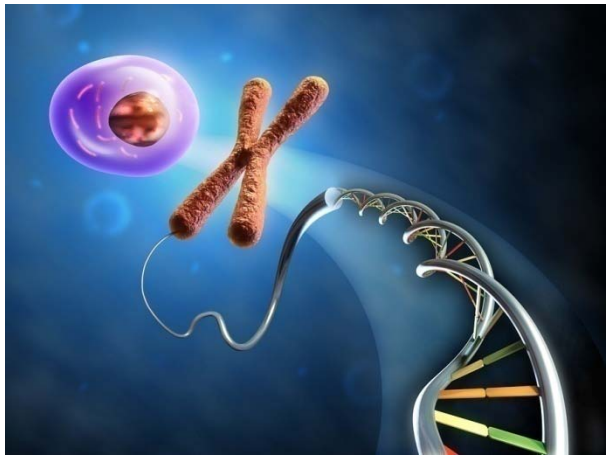
Single Hypothesis Testing

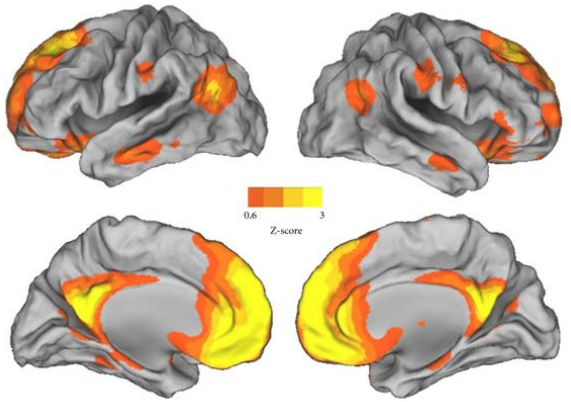
- In the past, a handful of hypotheses with a lot of samples, e.g. census data.
- H_0: $x = \mu$ vs. H_A: $x \neq \mu$
  - Are girls smarter than guys? => two sample t-test
  - Do last minute studying affect scores? => regression
- Generate statistics e.g. z, t, F, ...
- $p < 0.05$



Multiple Hypothesis Testing

- Nowadays, a lot of (unplanned) hypotheses but not enough samples (for medical research)





10^6

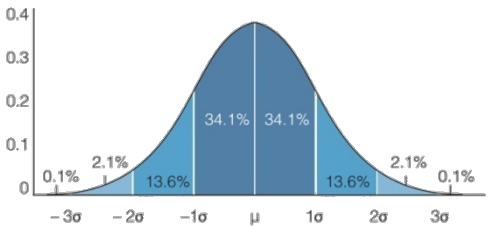
10^3 genomics

10^5

10^2 Neuroimaging

Multiple Testing Problem

- P(not rejecting 1 hypothesis) = 1- α
- P(not rejecting all n hypotheses) = $(1-\alpha)^n$
- $\alpha_{\text{FWER}} = 1-(1-\alpha)^n$
  - $\alpha = 0.05, n = 10$: $\alpha_{\text{FWER}} = 0.4013$
  - $\alpha = 0.05, n = 10^2$: $\alpha_{\text{FWER}} \approx 1$
- So if e.g. run 100 experiments, then $\alpha_{\text{FWER}} \cdot 100$ of them would have ≥1 hypothesis falsely rejected.
- Intuition from ML perspective is that the more we sample the variable space, the more "likely" we will get some "extreme" samples.



MATLAB Demo

Why Important?

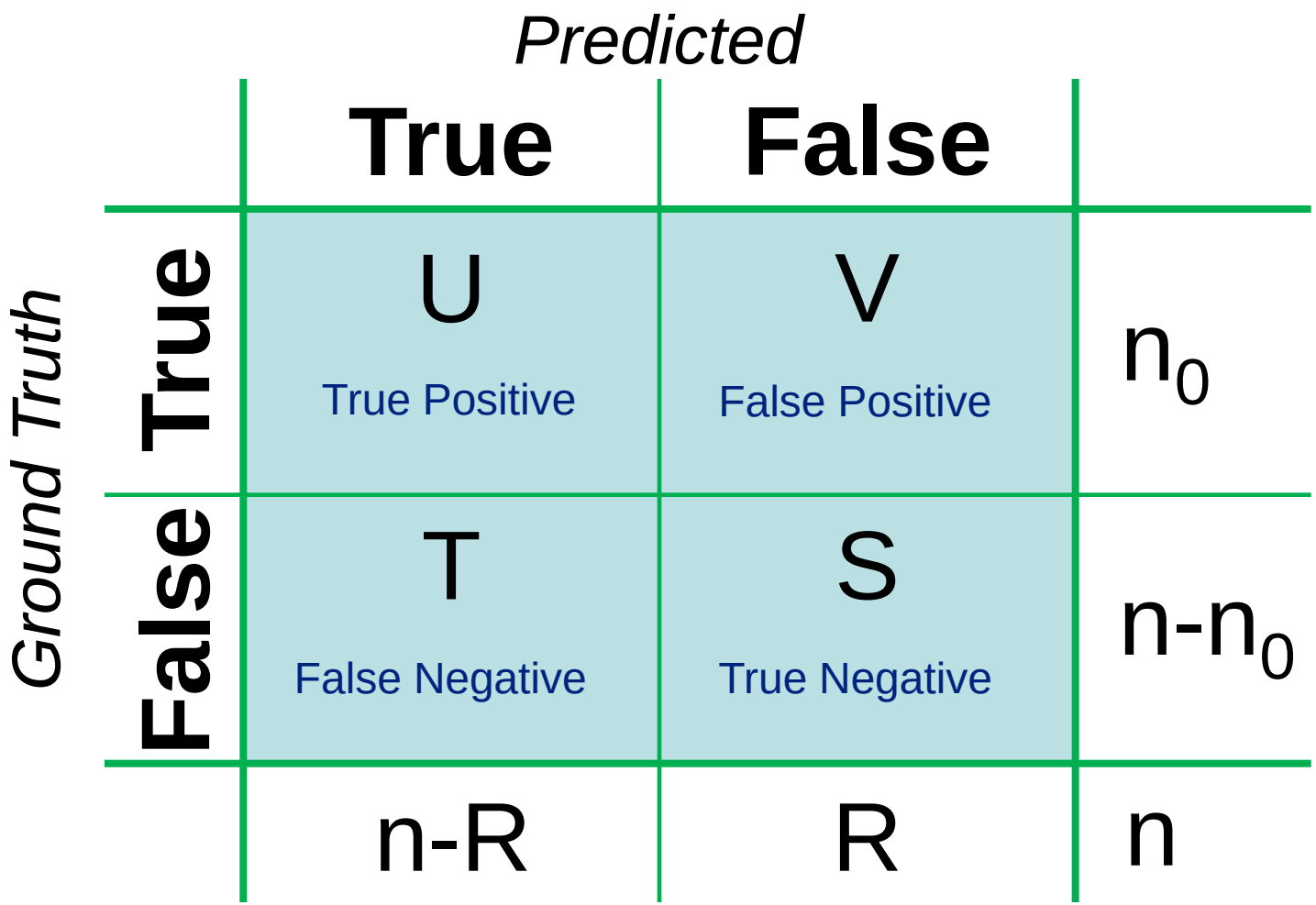
Problems with scientific research

How science goes wrong

Scientific research has changed the world. Now it needs to change itself

Last year researchers at one biotech firm, Amgen, found they could reproduce just **six of 53** "landmark" studies in cancer research. Earlier, a group at Bayer, a drug company, managed to repeat just a **quarter of 67** similarly important papers. A leading computer scientist frets that **three-quarters** of papers in his subfield are bunk. In 2000-10 roughly **80,000 patients** took part in clinical trials based on research that was **later retracted** because of mistakes or improprieties.

Notations and Terminologies



Sensitivity = $S/(n-n_0)$

Specificity = U/n_0

unobserved

Bonferroni Correction

Procedures

- Recall $\alpha_{\text{FWER}} = 1-(1-\alpha)^n$
- Set $\alpha = 1-(1-\alpha_{\text{FWER}})^{1/n} \approx 1-(1-\alpha_{\text{FWER}}/n) = \alpha_{\text{FWER}}/n$

Examples

- $\alpha_{\text{FWER}} = 0.05$ and $n = 10$, needs $\alpha = 0.05/10 = 0.005$
- $\alpha_{\text{FWER}} = 0.05$ and $n = 10^6$, needs $\alpha = 0.05/10^6 = 5 \times 10^{-8}$

Properties

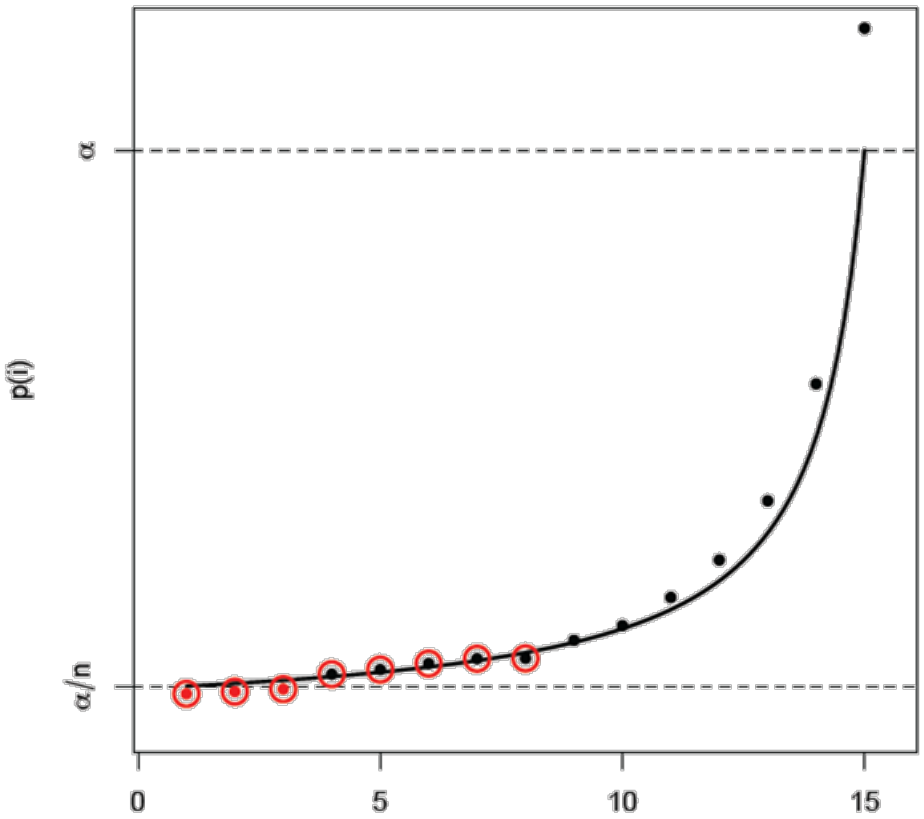
- Ctrls FWER = P(V≥1) in *strong* sense.
- Can handle correlated hypotheses.
- Very stringent

Ground Truth \ Predicted	True	False	
True	U	V	n_0
False	T	S	$n-n_0$
	n-R	R	n

MATLAB Demo

Step-up Procedure

- aka Hochberg's procedure
- Sort p in descending order
- $p(i) \leq \alpha/(n-i+1)$
  i. $p(n) \leq \alpha/(n-n+1)$
  ii. $p(n-1) \leq \alpha/(n-(n-1)+1)$
  iii. …
- Controls FWER in strong sense
- Holm's Step-down procedure uses same threshold but less sensitive.



MATLAB Demo

False Discovery Rate

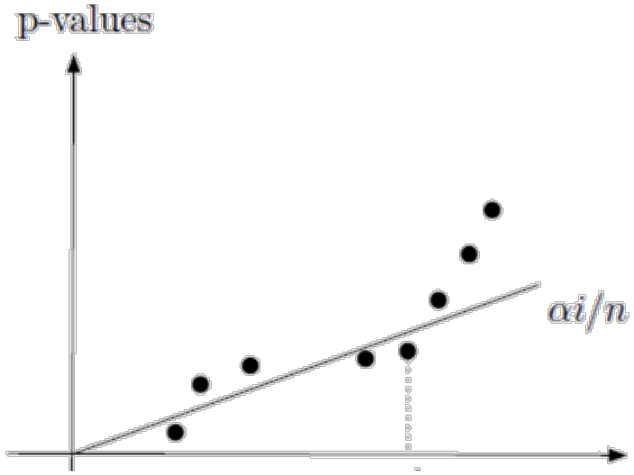
Idea

- Benjamini & Hochberg, 1995
- Recall FWER = P(V≥1)
- Fdp = V/max(R,1)
- But V unobserved, so: FDR = E(Fdp)

Ground Truth \ Predicted	True	False	
True	U	V	n_0
False	T	S	$n-n_0$
	n-R	R	n

Procedures

- Sort p in ascending order.
- Find i_0 = max i s.t. p(i) ≤ i·q/n



False Discovery Rate

Properties

- If hypotheses are independent, then FDR < q for *all* configurations of hypotheses.
- If data are Gaussian and hypotheses are positively correlated, i.e. $\sum_{ij} \geq 0$, then FDR < q.
- If hypotheses are correlated,

  FDR < q·(log(n)+0.577)
  => p(i) < i·q/n / (log(n)+0.577)

  BUT i = 1, p(i) < q/n / (log(n)+0.577) < q/n

		Predicted True	*Predicted* False	
Ground Truth	True	U	V	n_0
	False	T	S	$n-n_0$
		n-R	R	n

False Discovery Rate

Properties

- $n = n_0$, then FDR = FWER since:

  V=R, so V=0 iff Fdp = 0 and V≥1 iff Fdp=1,

  i.e. Fdp = indicator variable,

  thus P(V≥1) = E(Fdp) = FDR => ctrls FWER *weakly*

- $n < n_0$, controlling FWER controls FDR
- Adaptive: 5/100, 50/1000, …
- More sensitive than Hochberg

  i/n / (1/(n-i+1)) = i·(1-(i-1)/n)

  e.g. i = n/2 => ~n/4 gain

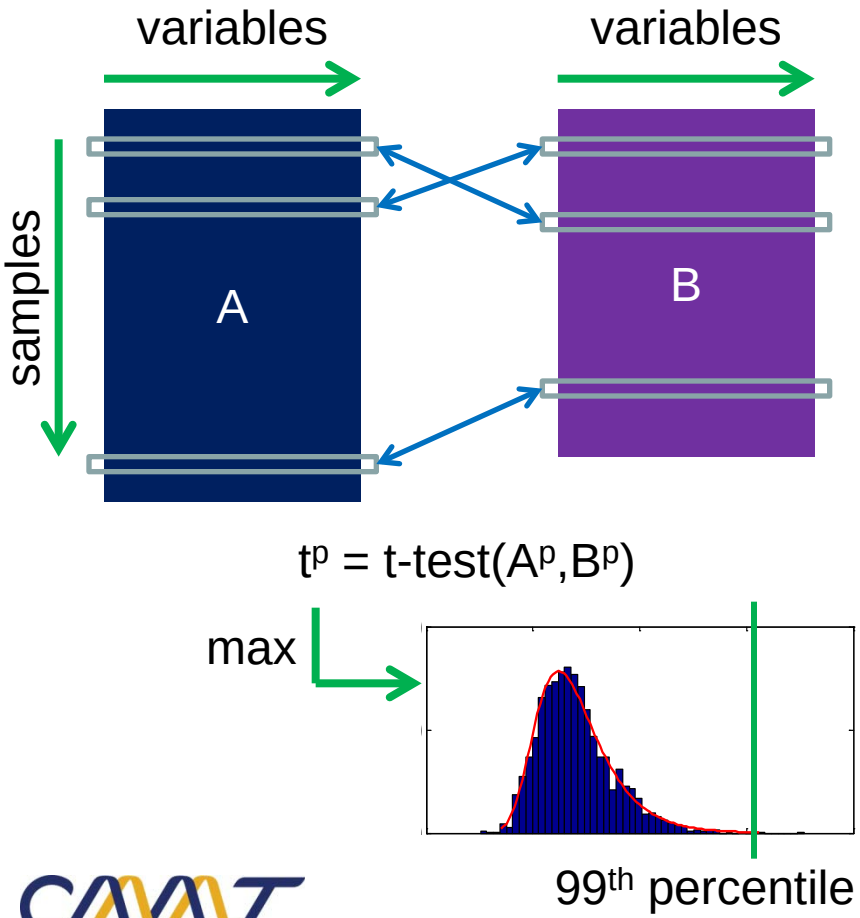
Ground Truth \ Predicted	True	False	
True	U	V	n_0
False	T	S	$n-n_0$
	n-R	R	n

MATLAB Demo

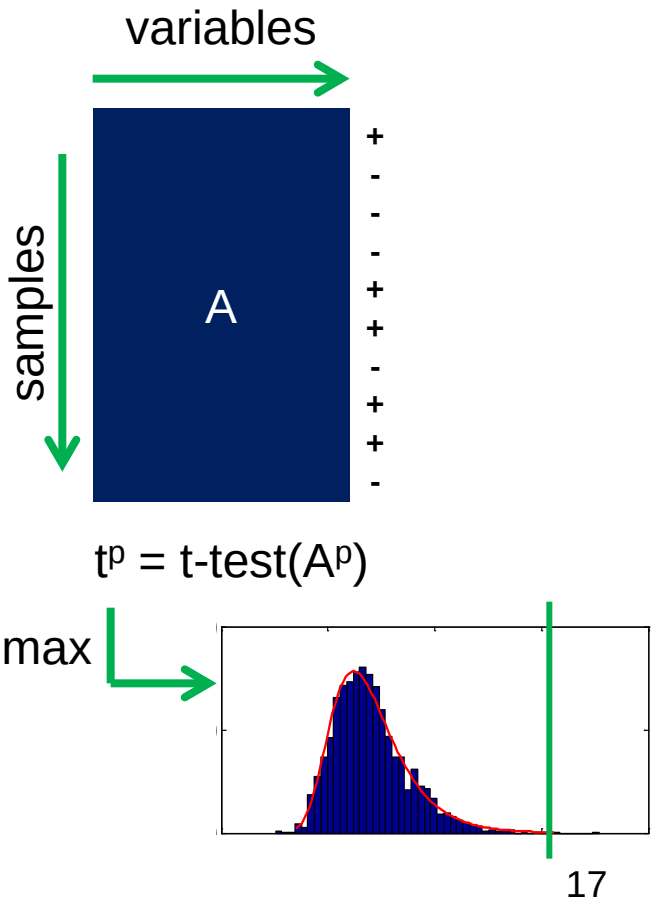
Max-t Permutation Test

- Strongly controls FWER under any kind of dependence structure under certain assumptions.

Two Sample



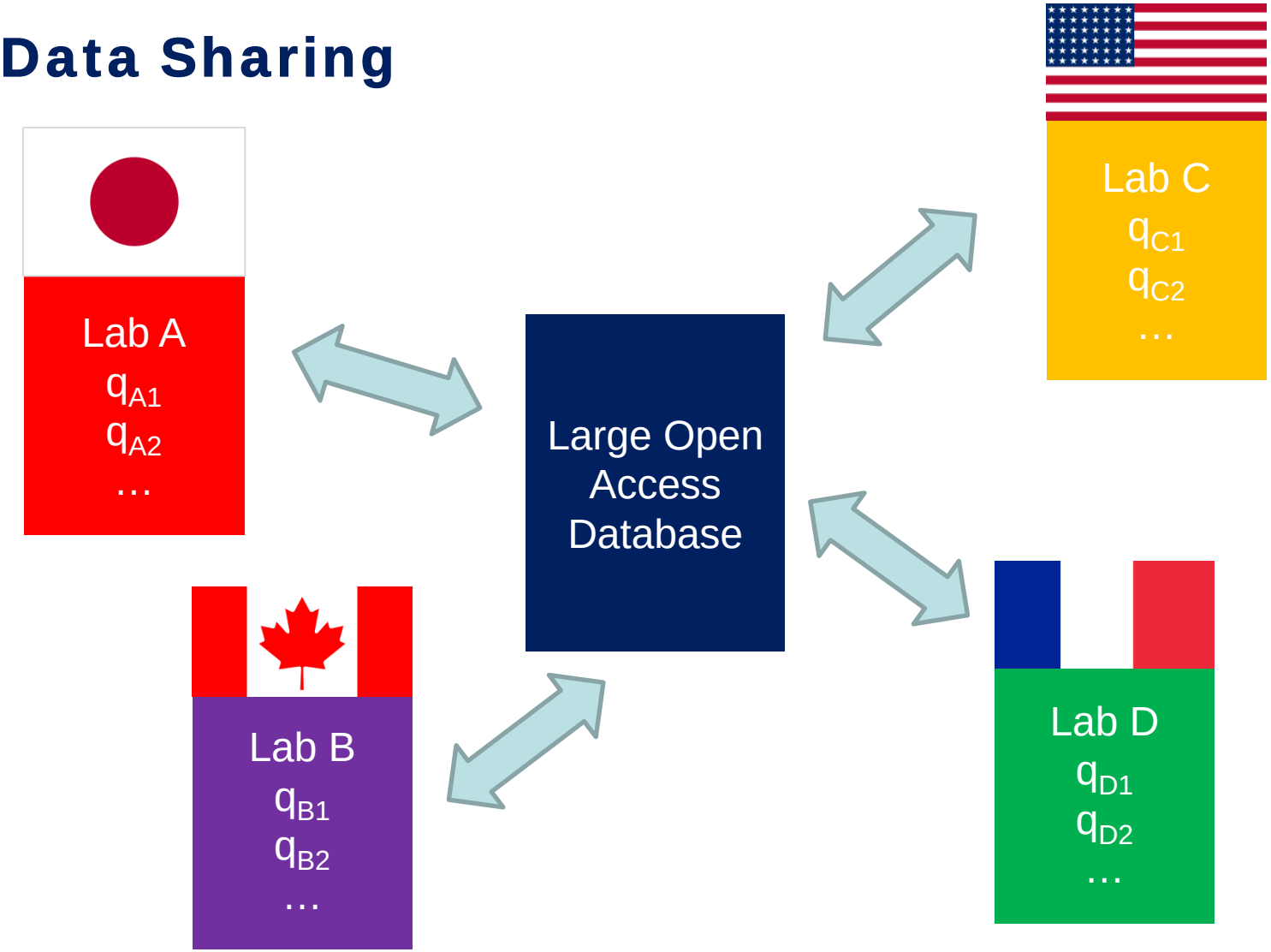
One Sample



MATLAB Demo

Recent Topics

- **Data Sharing**



Online FDR

Javanmard and Montanari, On Online Control of False Discovery Rate, 2015: arXiv:1502.06197

LORD (significance Levels based On Recent Discovery):

- Choose any sequence $\underline{\beta} = (\beta_i)_{i=1}^{\infty}$, such that

$$\beta_i \geq 0, \qquad \sum_{i=1}^{\infty} \beta_i = \alpha\,.$$

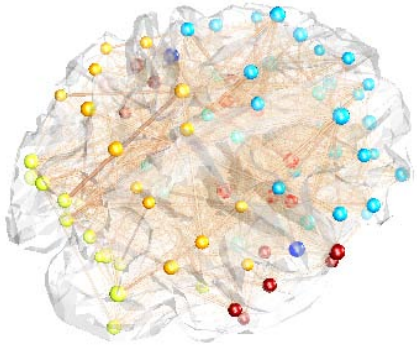
- Rule is given by

$$\tau_i \equiv \max\left\{\ell < i, H_\ell \text{ is rejected}\right\}.$$

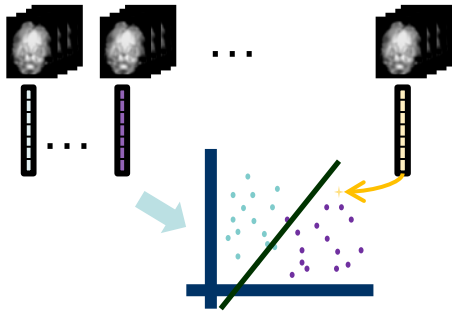
$$\alpha_i = \beta_{i-\tau_i}\,.$$

Neuroimaging Applications

Activation Detection

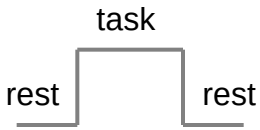


Connectivity Estimation

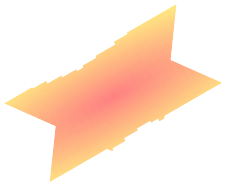


Brain Decoding

BOLD Effect

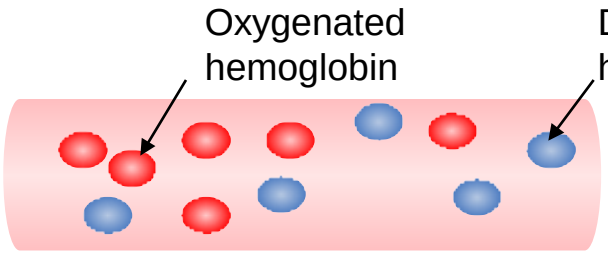


Stimulus



Neuron Firing

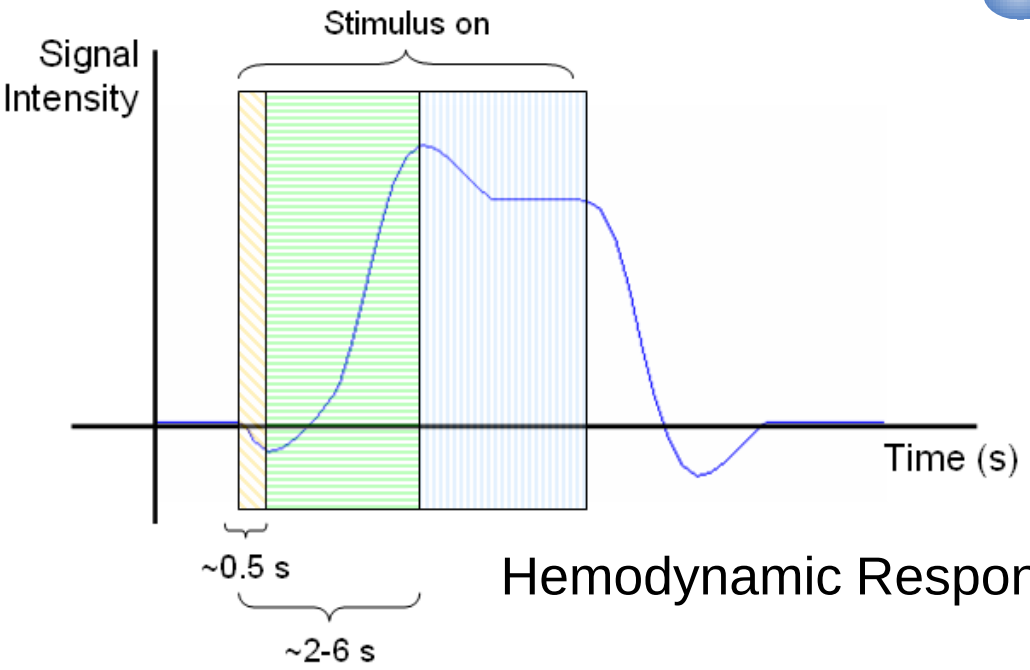
Oxygen Uptake



Oxygenated Blood Inflow

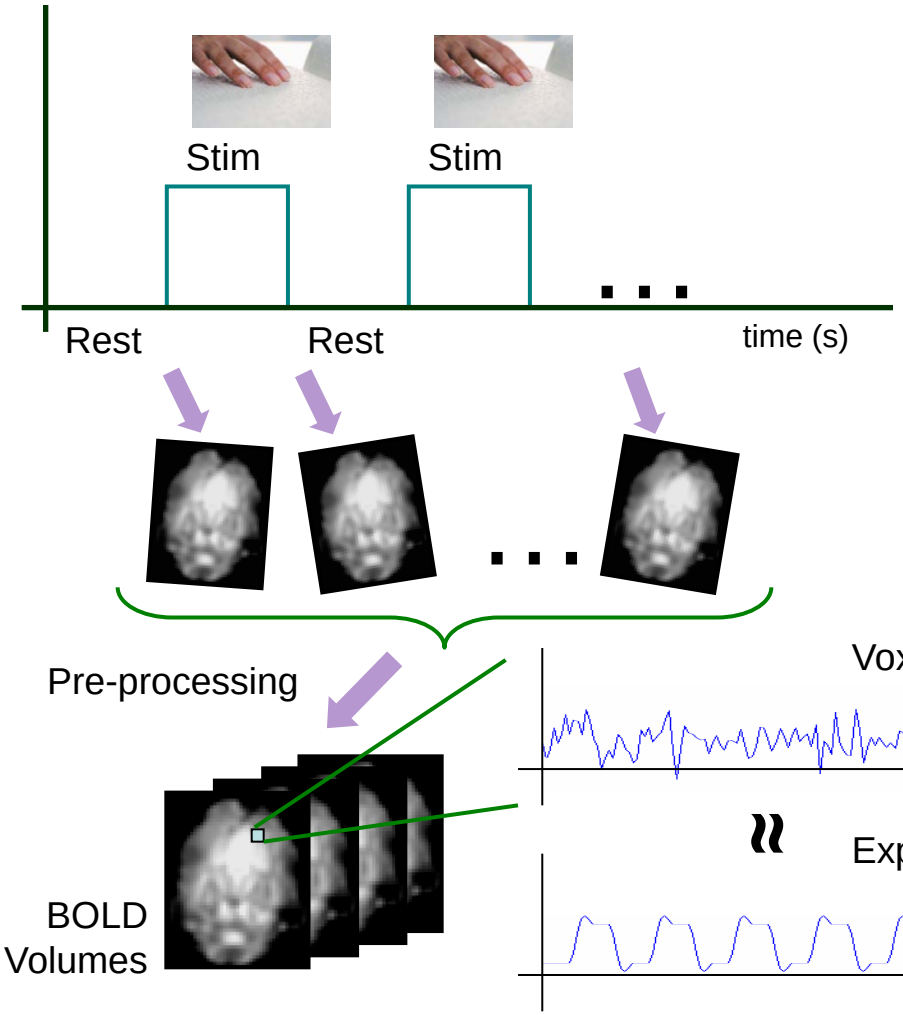
Diamagnetic

Paramagnetic



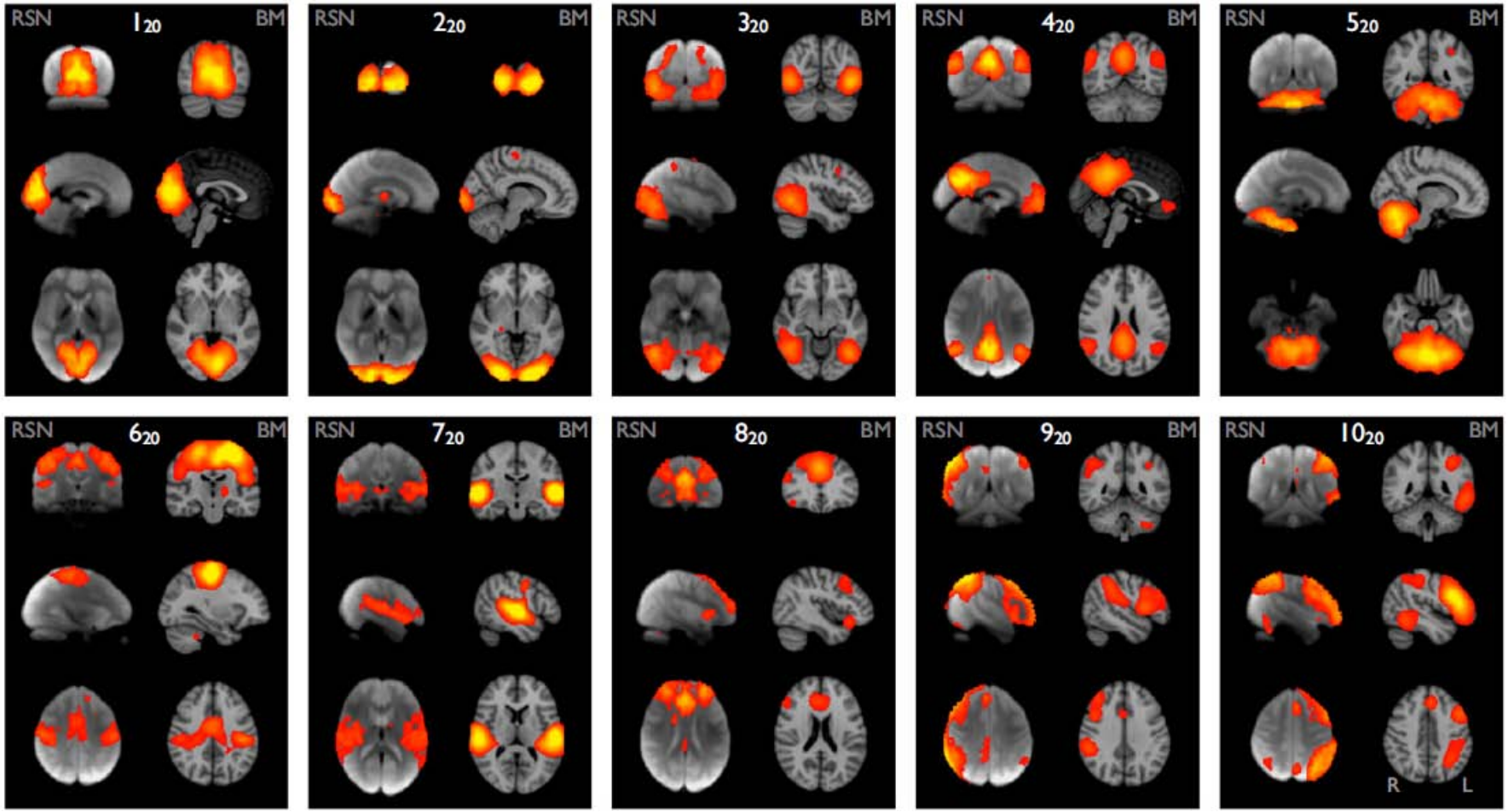
Hemodynamic Response

Task-based fMRI



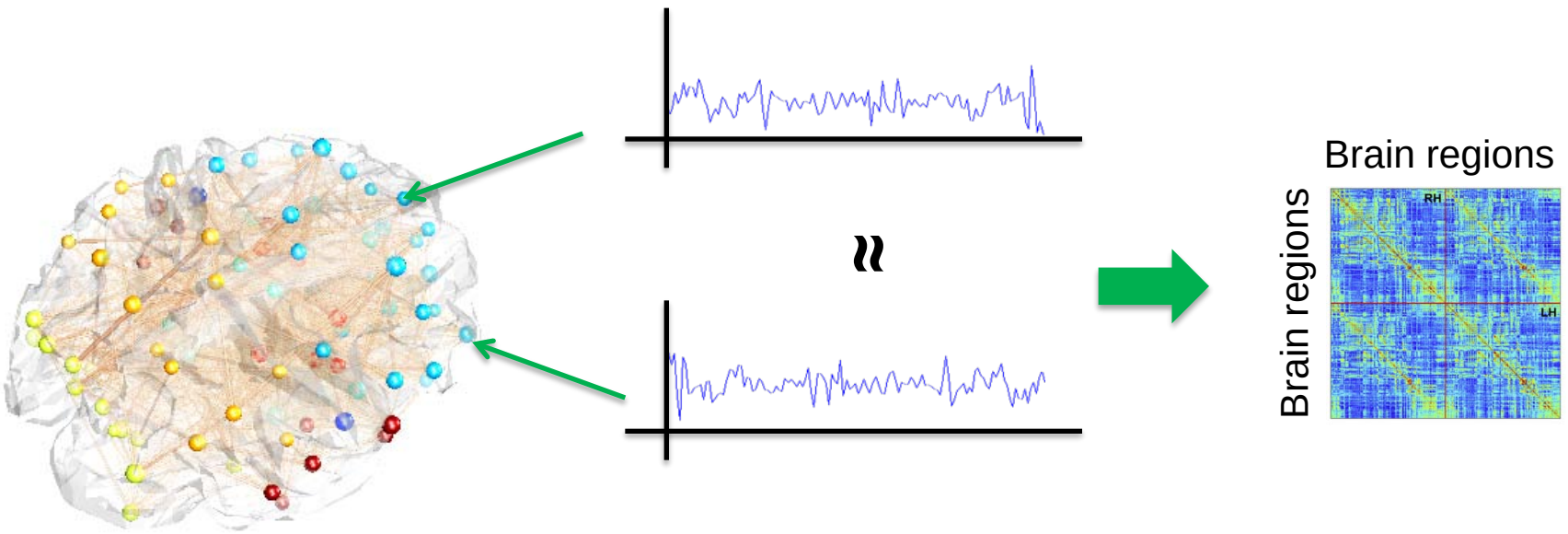
Activation
Statistics Maps

Resting State fMRI



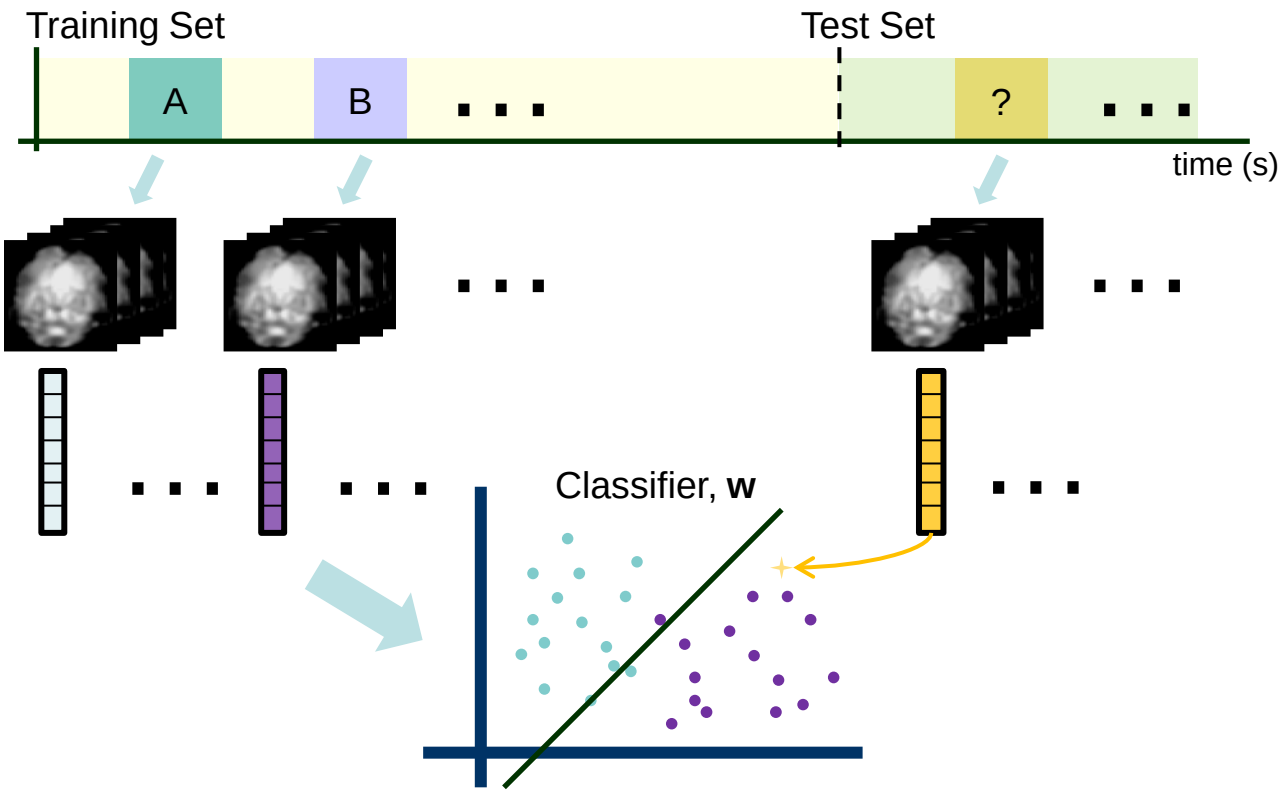
SM. Smith, P.T. Fox, K.L. Miller, D.C. Glahn, P.M. Fox, C.E. Mackay, N. Filippini, K.E. Watkins, R. Toro, A.R. Laird, and C.F. Beckmann, "Correspondence of the Brain's Functional Architecture During Activation and Rest," Proc. Natl. Acad. Sci., vol.106, pp.13040-13045, 2009

Connectivity Estimation



Which connection significant?

Brain Decoding



From **w**, which variable significantly drives classification?

Summary

- Multiple testing can result in many false findings if the number of tests is not accounted for.
- Bonferroni correction is too stringent.
- FDR correction is a good compromise.
- Data sharing is creating new problems.