Identifying Functional Co-Activation Patterns in Neuroimaging Studies Via Poisson Graphical Models

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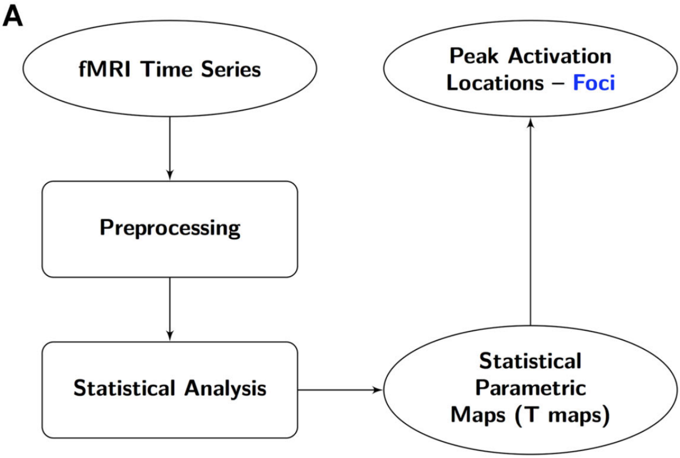
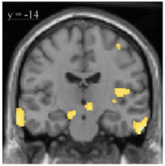
Outline

fMRI experiments pipeline



x	y	z
24	−79	13
30	−83	23
18	−96	23
−16	−96	18
−22	−90	−17
−36	−93	14



CBMA data & co-activation

B

Foci from Different Contrasts

Study	Contrast	Emotion	x	y	z
1	1	sad	-59	-14	-1
			...	...	...
			12	-74	-35
	2	happy	48	-78	-1
			...	...	...
			-57	-16	-2
2	3	anger	48	-74	-3
			...	....	...
			-24	0	-12
	4	sad	-57	-13	-2
			...	...	...
			14	-72	-32
	5	disgust	35	-80	15
			...	...	...
			-24	0	-12
...	....	...	...	...	...
164	437	fear	37	26	26
			...	...	...

Regional Foci Count

Contrast	Region 1	Region 2	....	Region 19
1	0	1	....	1
2	1	2	...	1
3	1	0	...	1
4	3	2	...	5
5	2	0	...	3
...	....	....	...	....
437	2	1	...	2

The Bivariate Poisson Model

- i, j are 2 regions in brain, k denotes contrasts
- $X_{i,k}, X_{j,k}$ the number of foci
- When $(X_{i,k}, X_{j,k}) \sim \mathrm{BP}(\lambda_{ii}, \lambda_{jj}, \lambda_{ij})$ then:
  - $X_{i,k} \sim \mathrm{Pois}(\lambda_{ii} + \lambda_{ij})$
  - $X_{j,k} \sim \mathrm{Pois}(\lambda_{jj} + \lambda_{ij})$
  - Pmf is:

$$P(X_{i,k} = x_{i,k}, X_{j,k} = x_{j,k})$$

$$= \mathrm{e}^{-(\lambda_{ii}+\lambda_{jj}+\lambda_{ij})} \frac{\lambda_{ii}^{x_{i,k}}}{x_{i,k}!} \frac{\lambda_{jj}^{x_{j,k}}}{x_{j,k}!} \sum_{s=0}^{\min(x_{i,k}, x_{j,k})} \binom{x_{i,k}}{s} \binom{x_{j,k}}{s} s! \left(\frac{\lambda_{ij}}{\lambda_{ii}\lambda_{jj}} \right)^s$$

Network detection

- Parameter $\boldsymbol{\lambda} = (\lambda_{ii}, \lambda_{jj}, \lambda_{ij})'$ fully describes network
- Covariance parameter λ_{ij} controls strength of co-activation
- A penalized likelihood framework is adopted:

$$\ell(\boldsymbol{\lambda}; \mathbf{X}_i, \mathbf{X}_j) - \theta\lambda_{ij}$$

- θ imposes sparsity on the network

Latent variable representation

- The likelihood of the model is computationally demanding
- Let $Y_{ij,k}$ be the total co-activations
- An alternative representation is:

$$X_{i,k} = Y_{ii,k} + Y_{ij,k}$$

$$X_{j,k} = Y_{jj,k} + Y_{ij,k}$$

- The complete model likelihood is then:

$$\ell_{\mathrm{comp}}(\boldsymbol{\lambda}; \mathbf{Y}_{ij}, \mathbf{X}_i, \mathbf{X}_j) - \theta\lambda_{ij}$$

- Now, the EM of Karlis (2003) can be used for estimation

Bivariate EM

- **E-step:**

$$Y_{ij,k}^{(t+1)} = E[Y_{ij,k} | X_{i,k}, X_{j,k}; \boldsymbol{\lambda}^{(t)}]$$

$$= \sum_{y_{ij,k}=0}^{\min(x_{i,k}, x_{j,k})} \frac{y_{ij,k} P(Y_{ij,k}, X_{i,k}, X_{j,k}; \boldsymbol{\lambda}^{(t)})}{\sum_{y_{ij,k}=0}^{\min(x_{i,k}, x_{j,k})} P(Y_{ij,k}, X_{i,k}, X_{j,k}; \boldsymbol{\lambda}^{(t)})}$$

- **M-step:**

$$\lambda_{ij}^{(t+1)} = \frac{\sum_{k=1}^{n} Y_{ij,k}^{(t+1)}}{\theta + n},$$

$$\lambda_{ll}^{(t+1)} = \frac{1}{n} \sum_{k=1}^{n} X_{l,k} - \frac{\theta + n}{n} \lambda_{ij}^{(t+1)} \qquad \text{for } l = i, j.$$

The multivariate case

- Only 2-way interactions considered here
- Similar arguments as with 2D model:

$$X_{i,k} = \sum_{j=1}^{p} Y_{ij,k} \quad i = 1 \ldots, p$$

- EM now minimizes:

$$-l_{\text{comp}}(\boldsymbol{\lambda}; \widetilde{\mathbf{Y}}_1, \ldots, \widetilde{\mathbf{Y}}_n, \mathbf{X}_1, \ldots, \mathbf{X}_n) + \theta \sum_{i=1}^{p} \sum_{j=i+1}^{p} \lambda_{ij}$$

$$= \sum_{k=1}^{n} \sum_{i=1}^{p} \sum_{j=i}^{p} [\lambda_{ij} - Y_{ij,k} \log(\lambda_{ij})] + \theta \sum_{i=1}^{p} \sum_{j=i+1}^{p} \lambda_{ij}.$$

Choice of tuning parameter

- Optimal value of θ is not known in practice
- Idea: split data in $X_{\text{train}}, X_{\text{test}}$ and use predictive log-likelihood:

$$l_{\text{obs}}(\hat{\boldsymbol{\lambda}}(\theta); \mathbf{X}_{\text{test}}) = \sum_{k=1}^{n} l_{\text{obs}}(\hat{\boldsymbol{\lambda}}(\theta); \mathbf{X}_{\text{test},k}).$$

- n-fold cross validation for many X_{test}

Testing significance

- 2 tests for significance of findings (non-zero covariances)
- Model detects networks but tests build on $\lambda_{ij}^{\mathrm{MLE}}$ **(no penalization)**
- Test I for pairs
  - $\mathcal{H}_0 : \lambda_{ij} = 0 \text{ vs } \mathcal{H}_1 : \lambda_{ij} > 0$
  - Contrast labels permuted for *p*-values
  - FDR applied
- Test II for full functional networks Φ
  - $\mathcal{H}_0 : \lambda_{ij} = 0, \ \forall \{i,j\} \in \Phi \quad \text{vs} \quad \mathcal{H}_1 : \exists \{i,j\} \in \Phi : \lambda_{ij} > 0$
  - Same permutation procedure as before

Simulation studies 1/3

- Setup 1: 3 regions, 300 datasets, 100 bootstrap replicates for s.e.:

$$\boldsymbol{\lambda} = \begin{bmatrix} 1 & 3 & 1 \\ & 2 & 5 \\ & & 3 \end{bmatrix}$$

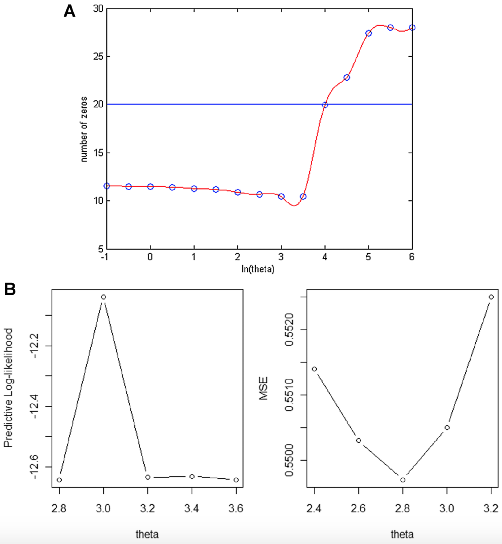
- Setup 2: 8 regions, 500 datasets:

$$\begin{array}{cccc} \lambda_{12} = 3 & \lambda_{15} = 4 & \lambda_{16} = 2 & \lambda_{27} = 2 \\ \lambda_{36} = 3 & \lambda_{48} = 4 & \lambda_{57} = 5 & \lambda_{78} = 1 \end{array}$$

Simulation studies 2/3

Bias (%)			Coverage rate		
Penalized multivariate Poisson model					
0.0020 (0.20%)	0.0019 (0.06%)	0.0115 (1.15%)	93.33%	95.00%	90.67%
	0.0142 (0.71%)	0.0024 (0.05%)		96.00%	95.00%
		0.0169 (0.56%)			95.00%
Covariance method					
0.1657 (16.57%)	0.0624 (2.08%)	0.1381 (13.81%)	92.00%	92.33%	91.67%
	0.0576 (2.88%)	0.1457 (2.91%)		96.33%	91.67%
		0.2747 (9.16%)			92.00%

Simulation studies 3/3

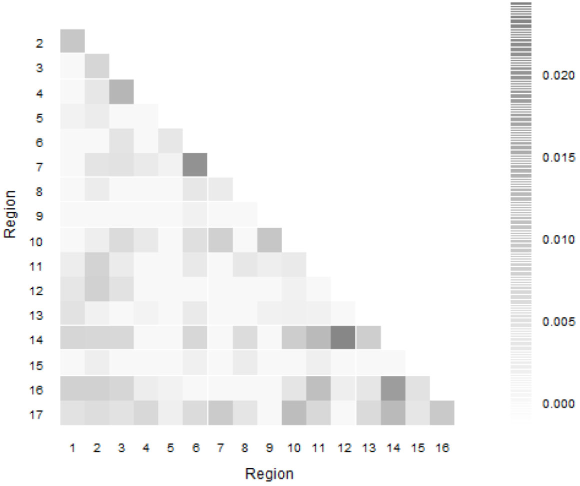


Data

- 437 contrasts from 162 studies of emotion (Kober et al, 2008)
- On average, 6 foci per contrast
- GSK CIC atlas based on Harvard-Oxford atlas
- 19 ROIs in total
    - Dorsolateral prefrontal cortex reported w.p. 0.5 (highest)
    - Right globus pallidus reported w.p. 0.007 (lowest)
    - Others reported w.p. 0.140 (average)

Results 1/4

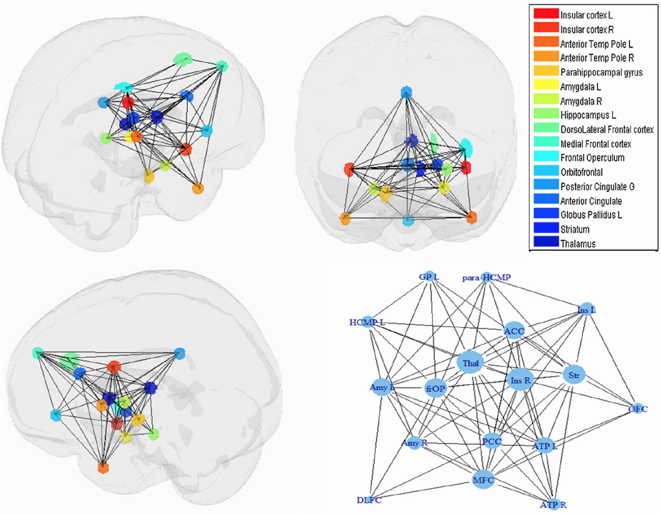
- Emotional processing network detected: 17 ROIs, 79 connections



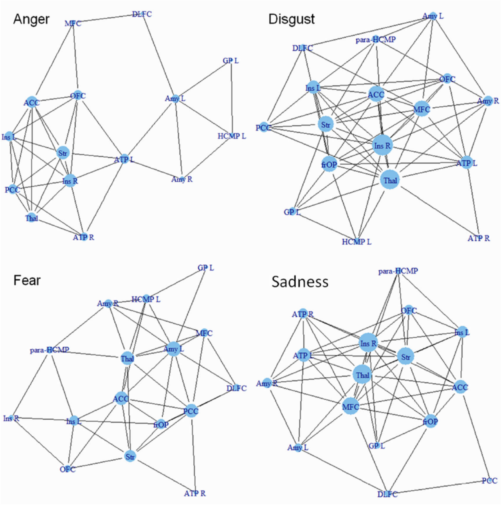
Results 2/4

- Anterior cingulate cortex (ACC) most connections: 11
  - Orbitofrontal cortex $\hat{\lambda}_{ij} = 0.023, p < 0.005$
  - Striatum $\hat{\lambda}_{ij} = 0.018, p < 0.005$
  - Thalamus $\hat{\lambda}_{ij} = 0.013, p < 0.005$
- Overall network significant as well $p < 0.005$
- Clustering coef. $C = 0.710$, path length $L = 1.129$
- Several regions with high degrees:
  - Right insular $D = 14$
  - Thalamus $D = 14$
  - Left amygdala $D = 11$

Results 3/4


Insular cortex L
Insular cortex R
Anterior Temp Pole L
Anterior Temp Pole R
Parahippocampal gyrus
Amygdala L
Amygdala R
Hippocampus L
DorsoLateral Frontal cortex
Medial Frontal cortex
Frontal Operculum
Orbitofrontal
Posterior Cingulate G
Anterior Cingulate
Globus Pallidus L
Striatum
Thalamus
GP L
para HCMP
Ins L
HCMP L
ACC
Thal
Str
Ins R
Amy L
frOP
OFC
Amy R
PCC
ATP L
MFC
DLFC
ATP R

Results 4/4



Discussion

- Pros:
  - New tool for CBMA data
  - Likelihood based
  - Nice intepretability
- Cons:
  - Brain tessellation may be subjective
  - No 3-way (or more) interactions
  - No voxel-wise rates

THANK YOU!!!