

# Got ROIs?

## Efficient Modeling through Information Pooling

afni26\_ROI-based-modeling.pdf

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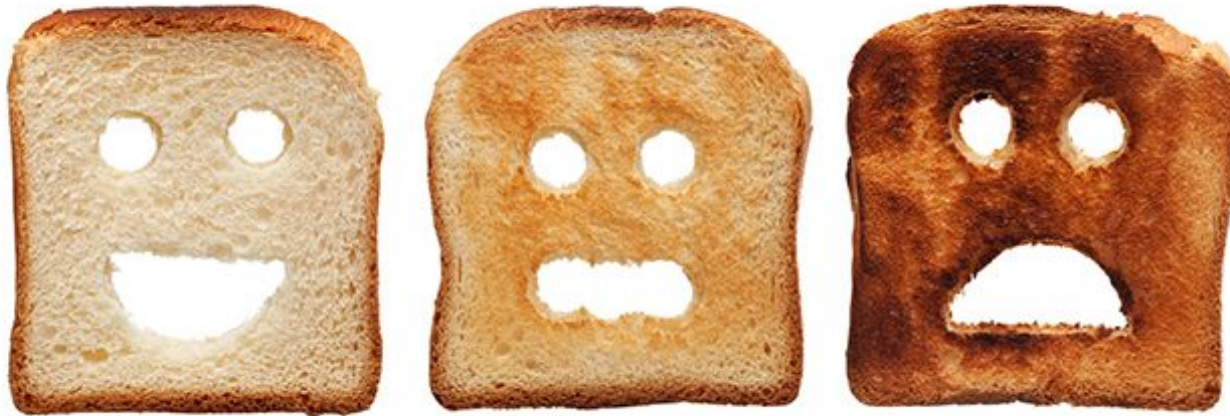
National Institutes of Health, USA



# Preview

- **Efficient modeling through information pooling**
  - How to effectively avoid multiplicity penalty?
- **Demo dataset #1**
  - Resting state: seed-based correlation analysis
  - Handling multiple testing through **ROI-based group analysis**
    - How to avoid penalty of modeling across voxels or ROIs?
  - Program available in **AFNI: BayesianGroupAna.py**
- **Demo dataset #2**
  - Group analysis with correlation matrices among ROIs
  - Handling multiple testing for **inter-region data (IRD) analysis**
    - How to avoid penalty of modeling across voxels or ROIs?
  - More applications
    - **DTI data: white matter connectivity network**
    - **Naturalistic data analysis**

Are you eating acrylamide for breakfast?



Both sides good

One side **BURNT**

Both sides **BURNT**

- Conditional probability
- Knowledge updating

# Conventional Statistical Framework: NHST

- **Two types of errors: null hypothesis significance testing (NHST)**

- What is  $H_0$  in FMRI studies?  $H_0$  = no effect (activation, difference, ...) at a voxel
- **Type I error** = Prob(reject  $H_0$  when  $H_0$  is true) = false positive =  $p$  value
- **Type II error** = Prob(accept  $H_0$  when  $H_1$  is true) = false negative =  $b$
- **power** =  $1 - b$  = probability of detecting true activation
- Goal: control type I error rate while increasing power (decreasing type II errors)
- Significance level  $\alpha$  (magic number 0.05) :  $p < \alpha$

		Justice System: Trial		Statistics: Hypothesis Test	
		Hidden Truth		Hidden Truth	
		Defendant Innocent	Defendant Guilty	$H_0$ True Not Activated	$H_0$ False Activated
Reject Presumption of Innocence (Guilty Verdict)		<b>Type I Error</b> (defendant very unhappy)	Correct	<b>Type I Error</b> (false positive)	Correct
Fail to Reject Presumption of Innocence (Not Guilty Verdict)		Correct	<b>Type II Error</b> (defendant very happy)	Correct	<b>Type II Error</b> (false negative)
				Reject $H_0$ (decide voxel is activated)	Don't Reject $H_0$ (decide voxel isn't activated)

## Problems with NHST

- World is not always discretely YES or NO
  - Dichotomous: Guilt vs. Innocence (mostly)
  - Not dichotomous (“activate” vs. “inactivate”) in a brain region
    - Real data for effect estimates are not 0s in the brain
    - Practical goal: what is strength of evidence for a claim?
- **Straw man**: null hypothesis – **witch hunt**
  - $H_0$ : scientifically uninteresting; unrealistic characterization of brain regions (especially *en masse*)
  - “False positive”: dichotomous misnomer for real data
- Interpretation: conditional probability  $P(\text{evidence} \mid H_0)$ 
  - $p(\text{evidence} \mid H_0) \neq p(H_0 \mid \text{data})$  ! 😊
- Abusive interpretation
  - Statistically insignificant = Non-existing effect?
  - Choose a voxelwise threshold (e.g., 0.001) and be “done”

# Problems with NHST

- **Thresholding under NHST: dichotomized decision**
  - $p$ -value of 0.05 vs 0.051, or cluster size of 54 vs 53 voxels
  - Difference between “significant” & “insignificant” results
  - Selection bias about effect estimates in results reporting
    - Power analysis based on literature: not very useful
    - One source of reproducibility problem
    - Unreliable meta analyses (many effects get lost)
- **Cluster thresholding – “iceberg above water” approach**
  - Using spatial extent as a leverage to control false positives
  - Cluster threshold of 54 voxels: cannot report 53 voxels?
  - Penalizing anatomically small regions: **discrimination!**
    - **Unfair:** 2 regions with same signal strength: 1 large and 1 small size
    - 2 regions with same signal strength: 1 case (distant) and 1 case (contiguous)
  - Sidedness for whole brain: one- or two-sided?

# Appetizer #1: everybody loves GLM!

## • Dataset #1

- Subjects:  $n = 124$  children; resting-state data
- Individual subjects: seed-based correlation for each subject
  - 3D correlation between seed and whole brain (“functional connectivity”)
- Explanatory variable (behavior data): Theory of Mind Index  $x_i$

## • Voxel-based group analysis: GLMs

- Focus: association between and seed-based correlation (z-score)
- **Pretense**: voxels **unrelated**

- GLMs: mass univariate  
 $m = 100,000$  voxels  $\rightarrow$   
 $m = 100,000$  models

$$\text{1st voxel: } z_1 = a_1 + b_1 \mathbf{x} + \epsilon_1$$

$$\text{2nd voxel: } z_2 = a_2 + b_2 \mathbf{x} + \epsilon_2$$

...

$$\text{mth voxel: } z_m = a_m + b_m \mathbf{x} + \epsilon_m$$

# GLMs: dealing with multiplicity!

- **Voxel-based group analysis: GLMs**

- **Penalty time** for pretense: multiple testing ( $m = 100,000$ ), magic **0.05**
- **Show time** for various correction methods
  - Voxel-wise  $p$ , FWE, FDR, spatial smoothness, clusters, ...
  - Simulations, random field theory, permutations, ...
  - How would dataset turn out under GLM? **4 lucky clusters** manage to survive

voxel $p$	cluster threshold	surviving ROIs	ROIs
0.001	28	2	R PCC, PCC/PrC
0.005	66	4	R PCC, PCC/PrC., L IPL, L TPJ
0.01	106	4	R PCC, PCC/PrC., L IPL, L TPJ
0.05	467	4	R PCC, PCC/PrC., L IPL, L TPJ



# Switching from voxels to ROIs: **motivations**

- **Motivations of ROI-based approach**
  - Avoiding arbitrary thresholding and clustering
  - No discrimination against small regions
  - All regions judged by their strength, not physical size
- **ROI definitions**
  - Anatomical atlases
  - Functional parcellations
  - Previous studies
  - Split current data
    - Part for localization and ROI definition, part for ROI-based analysis

# Switching from voxels to ROIs: **still GLMs**

- **ROI-based group analysis : GLMs**

- Focus: association between and seed-based correlation (z-score)

- **Pretense**: ROIs **unrelated**

- GLMs: mass univariate

$m = 100$  ROIs  $\rightarrow$

$m = 100$  models

- **Penalty time** for pretense:  
multiple testing – what to do?

- **Bonferroni**? Unbearable
- What else?

$$\text{1st ROI: } z_1 = a_1 + b_1 \mathbf{x} + \epsilon_1$$

$$\text{2nd ROI: } z_2 = a_2 + b_2 \mathbf{x} + \epsilon_2$$

...

$$\text{mth ROI: } z_m = a_m + b_m \mathbf{x} + \epsilon_m$$

# Switching from GLMs to LME

- ROI-based group analysis : Linear Mixed-Effects modeling

- One model integrates all ROIs
- ROIs loosely constrained instead of being unrelated
  - Gaussian distribution: Is it far-fetched?
  - Similar to cross-subject variability

- Goal: effect of interest  $b + \beta_j$

- Fixed vs. random effects?

- What can we get out of LME?

- Estimates for fixed effects
- Variances for random effects

- Cul-de-sac!**

Overall effect:  
shared by all ROIs  
and subjects

Effect by  
 $i$ th subject

Unique effect  
by  $j$ th ROI

$$z_{ij} = a + bx_i + \pi_i + \alpha_j + \beta_j x_i + \epsilon_{ij}$$

$$\pi_i \stackrel{iid}{\sim} \mathcal{N}(0, \tau^2), (\alpha_j, \beta_j)^T \stackrel{iid}{\sim} \mathcal{N}(\mathbf{0}, \boldsymbol{\lambda})$$

$$\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2), i = 1, 2, \dots, n, j = 1, 2, \dots, m$$

# One more jump from LME to **BML**

- **ROI-based group analysis : Bayesian Multi-Level modeling**

- **One** model integrates all ROIs: same as LME, but under Bayesian

- ROIs loosely **constrained** instead of being **unrelated**

- Gaussian distribution: is it far-fetched?
- Similar to cross-subject variability

- Goal: effect of interest  $b + \beta_j$

- Same model as LME plus **priors**

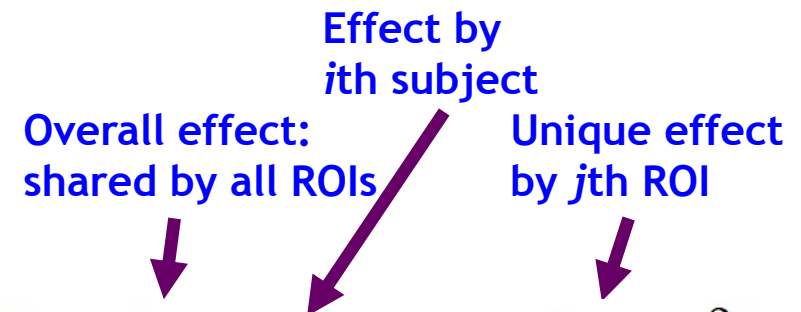
- **Markov chain Monte Carlo (MCMC)**
- Inferences via posterior distribution

- ***Ka-ching!***

$$y_{ij}|x_i, a, b, \pi_i, \alpha_j, \beta_j \sim \mathcal{N}(a + bx_i + \pi_i + \alpha_j + \beta_j x_i, \sigma^2)$$

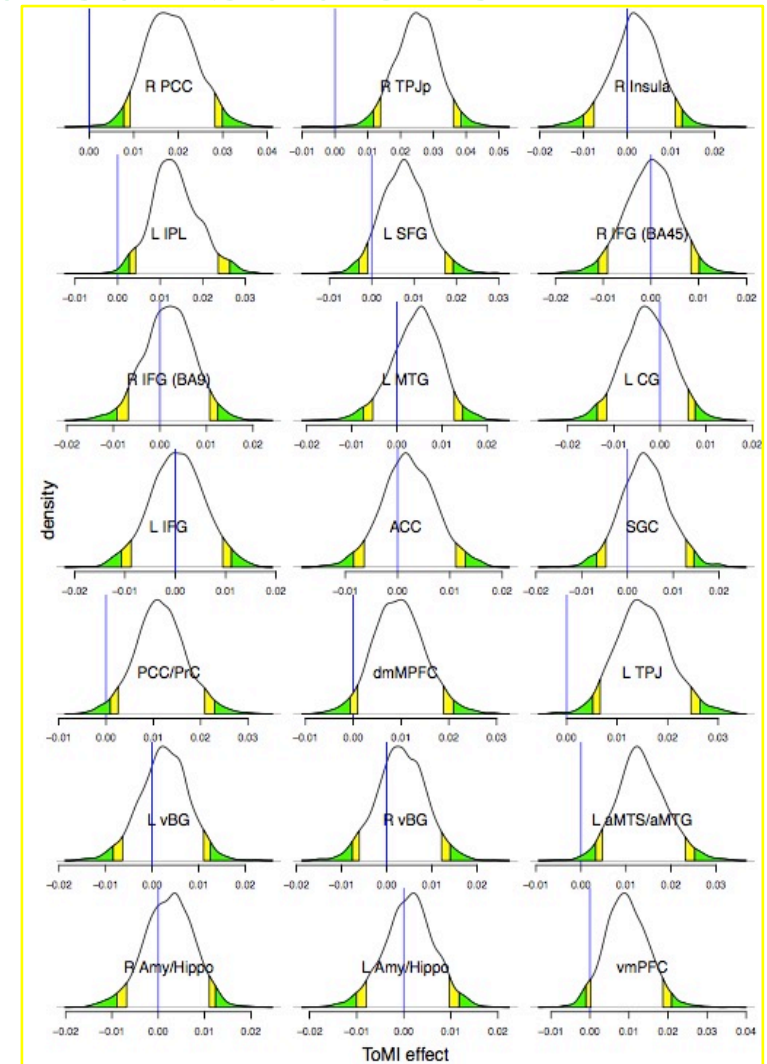
$$\pi_i \sim \mathcal{N}(0, \tau^2), (\alpha_j, \beta_j)^T \sim \mathcal{N}((0, 0)^T, \boldsymbol{\lambda})$$

$$i = 1, 2, \dots, n, j = 1, 2, \dots, m$$



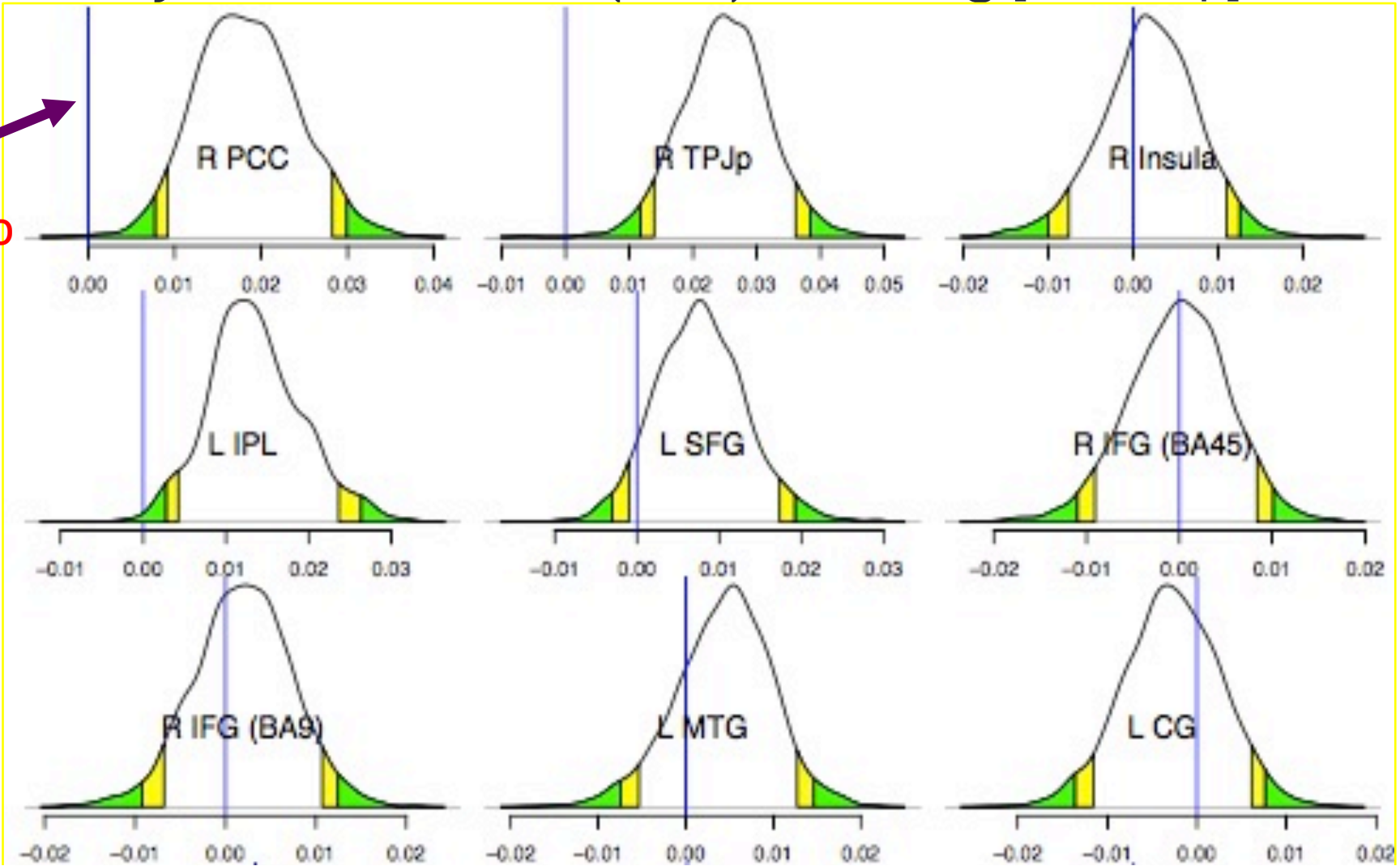
# Inferences from BML: full distributions

- ROI-based BML: 21 ROIs
- Full report with richer information: posterior distributions for each ROI
  - No dichotomization
  - No results hiding
  - No discrimination against small regions
- 8 ROIs with strong evidence of effect compared to
  - ROI-wise GLM with Bonferroni
  - Voxel-wise GLM at cluster level



# Bayesian Multilevel (BML) Modeling [blown up]

Blue  
Line:  
effect  
of ZERO



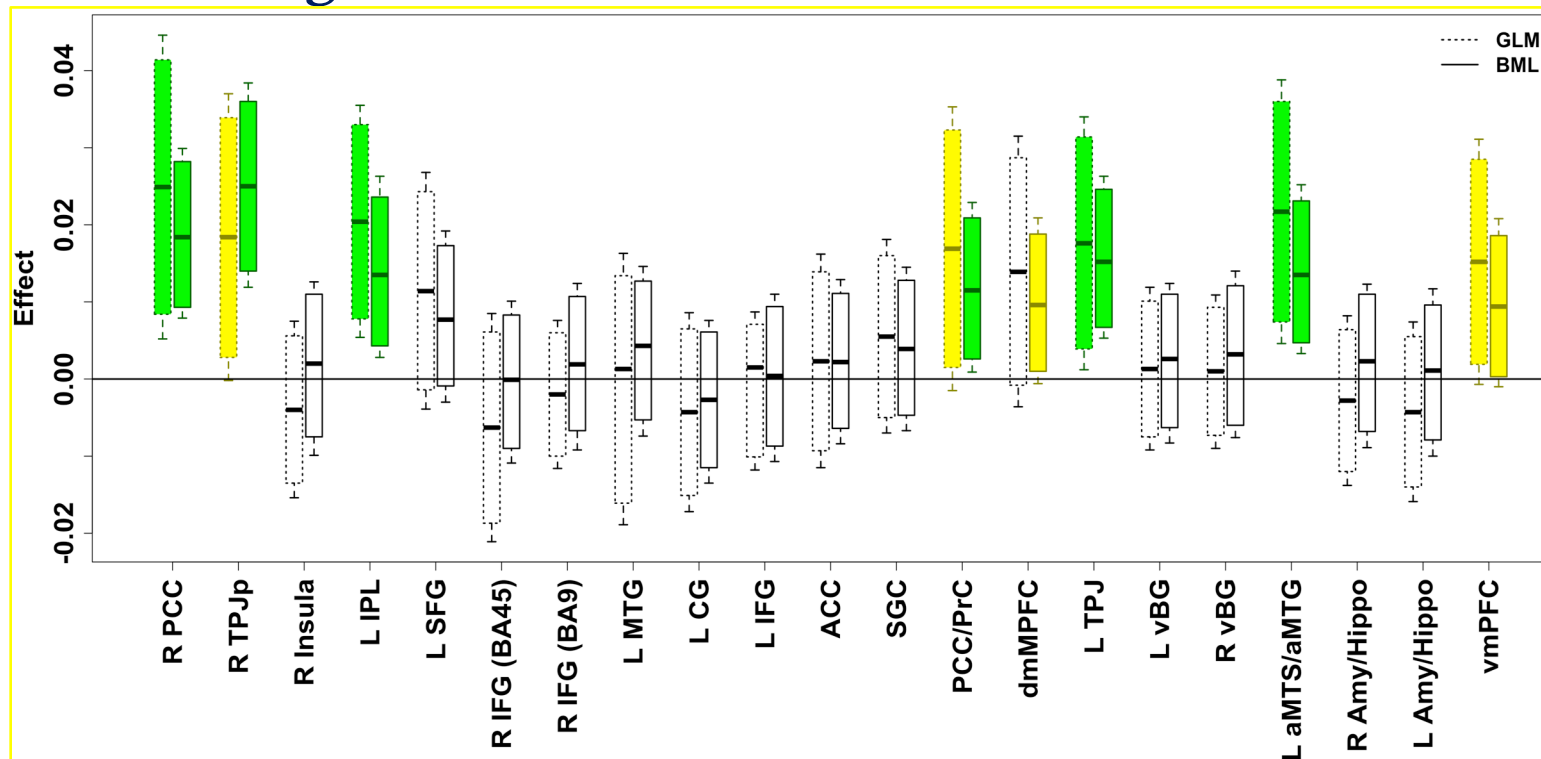
# Inferences from BML: **quantile interval**

- ROI-based BML: 21 ROIs
- full report with a table of quantile intervals
- **8 ROIs** with strong evidence for effect of interest

ROI \ result	ToMI effect		standard error		2.5%		5%		95%		97.5%	
	GLM	BML	GLM	BML	GLM	BML	GLM	BML	GLM	BML	GLM	BML
R PCC	0.025	0.018	0.010	0.006	0.005	0.008	0.008	0.009	0.041	0.028	0.045	0.030
R TPJp	0.018	0.025	0.009	0.007	-0.000	0.012	0.003	0.014	0.034	0.036	0.037	0.038
R Insula	-0.004	0.002	0.006	0.006	-0.015	-0.010	-0.014	-0.008	0.006	0.011	0.007	0.013
L IPL	0.020	0.014	0.008	0.006	0.005	0.003	0.008	0.004	0.033	0.024	0.035	0.026
L SFG	0.011	0.008	0.008	0.006	-0.004	-0.003	-0.001	-0.001	0.024	0.017	0.027	0.019
R IFG (BA45)	-0.006	0.000	0.007	0.005	-0.021	-0.011	-0.019	-0.009	0.006	0.008	0.008	0.010
R IFG (BA9)	-0.002	0.002	0.005	0.005	-0.012	-0.009	-0.010	-0.007	0.006	0.011	0.008	0.012
L MTG	-0.001	0.004	0.009	0.005	-0.019	-0.007	-0.016	-0.005	0.013	0.013	0.016	0.015
L CG	-0.004	-0.003	0.007	0.005	-0.017	-0.014	-0.015	-0.011	0.007	0.006	0.009	0.008
L IFG	-0.002	0.000	0.005	0.005	-0.012	-0.011	-0.010	-0.009	0.007	0.009	0.009	0.011
ACC	0.002	0.002	0.007	0.005	-0.012	-0.008	-0.009	-0.006	0.014	0.011	0.016	0.013
SGC	0.006	0.004	0.006	0.005	-0.007	-0.007	-0.005	-0.005	0.016	0.013	0.018	0.014
PCC/PrC	0.017	0.012	0.009	0.005	-0.001	0.001	0.002	0.003	0.032	0.021	0.035	0.023
dmMPFC	0.014	0.010	0.009	0.005	-0.004	-0.001	-0.001	0.001	0.029	0.019	0.032	0.021
L TPJ	0.018	0.015	0.008	0.005	0.001	0.005	0.004	0.007	0.031	0.025	0.034	0.026
L vBG	0.001	0.003	0.005	0.005	-0.009	-0.008	-0.007	-0.006	0.010	0.011	0.012	0.012
R vBG	0.001	0.003	0.005	0.005	-0.009	-0.008	-0.007	-0.006	0.009	0.012	0.011	0.014
L aMTS/aMTG	0.022	0.013	0.009	0.006	0.005	0.003	0.007	0.005	0.036	0.023	0.039	0.025
R Amy/Hippo	-0.003	0.002	0.006	0.005	-0.014	-0.009	-0.012	-0.007	0.006	0.011	0.008	0.012
L Amy/Hippo	-0.004	0.001	0.006	0.005	-0.016	-0.010	-0.014	-0.008	0.005	0.010	0.007	0.012
vmPFC	0.015	0.009	0.008	0.006	-0.001	-0.001	0.002	0.000	0.029	0.019	0.031	0.021

# Inferences from BML: **standard error**

- ROI-based BML: 21 ROIs
- full report with **bar graph** quantile intervals (better visualization)
  - **Nothing hidden under sea level**
- 8 ROIs with strong evidence for effect of interest





# BML: model validations

- ROI-based BML with 21 ROIs: cross-validation

- Leave-one-out information criterion (LOOIC)

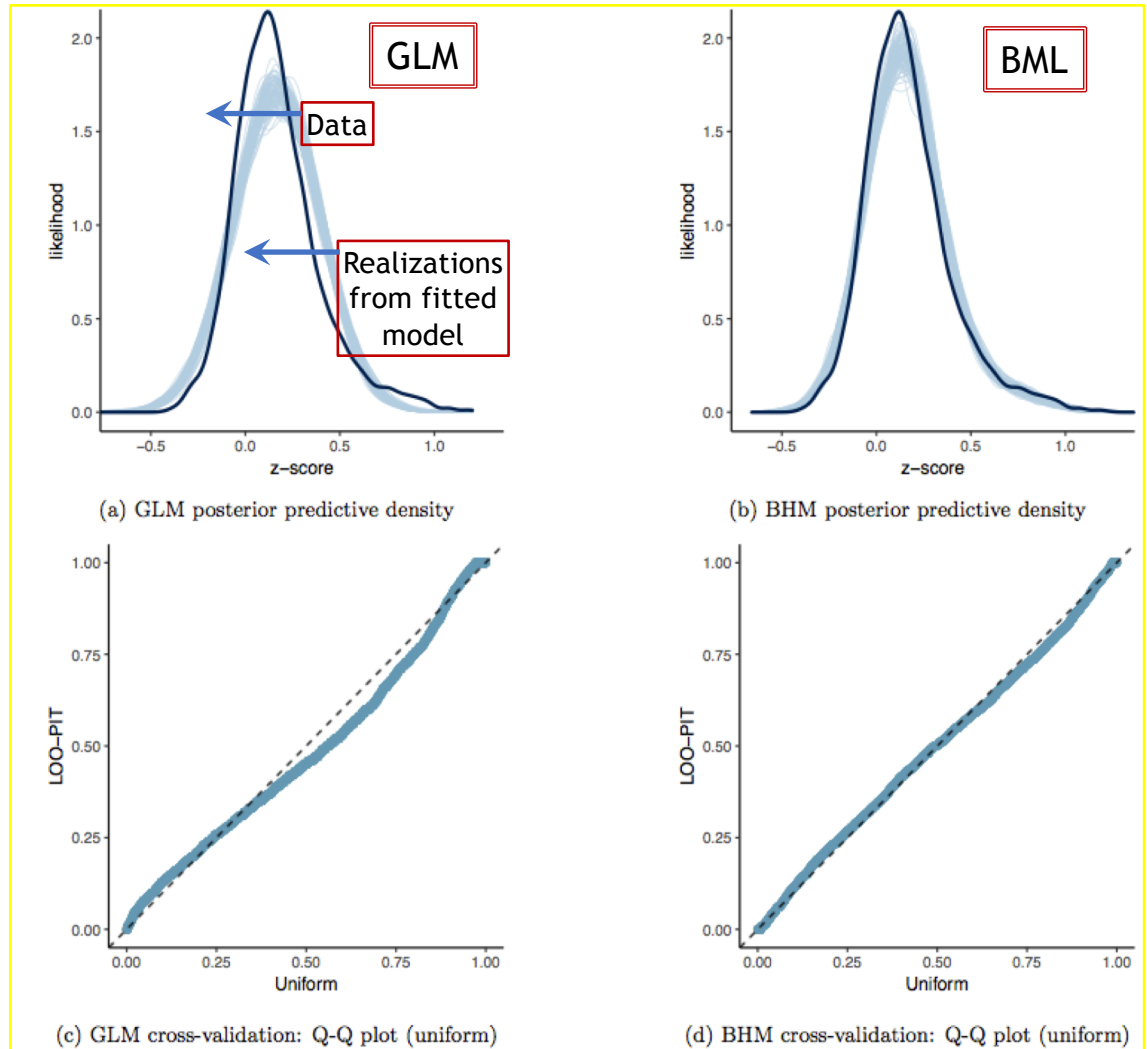
### Cross-validation

	LOOIC	SE
GLM	-300.39	98.25
BML	-2247.06	86.42
GLM - BML	1946.67	96.35

- Posterior predictive checking

- Effects of BML

- Regularizing ROIs: don't fully trust individual ROI data
  - Sacrificing fit at each ROI; achieving better overall fit



## Appetizer #2: more love for GLM!

- **Dataset #2: correlation matrix**

- Subjects:  $n = 41$  children; response-conflict task
- Individual subjects: **correlation matrix** among  $m = 16$  ROIs
- How to go about group analysis?
  - **GLM for each element in correlation matrix**
  - **Binarization approach: graph theory**
- More broadly: matrix-based analysis (MBA) (“network modeling”)
  - **Inter-region correlation (IRC)**
  - **Structural attribute matrix (SAM)**

- **Focus on GLM**

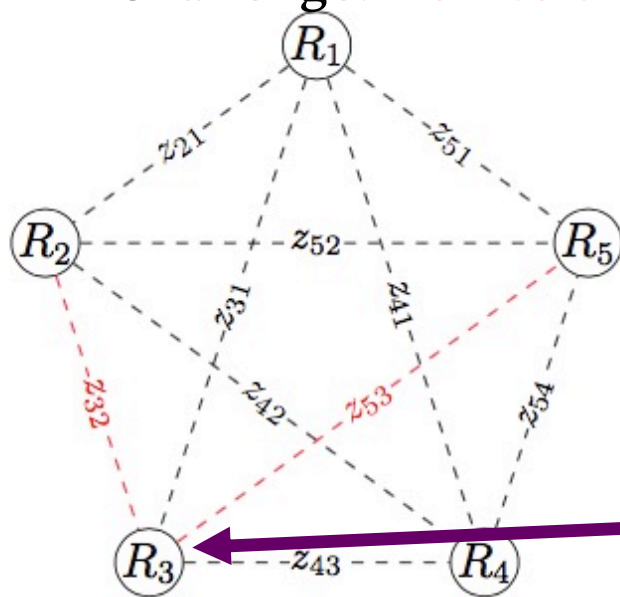
- Student  $t$ -test or GLM on each element
  - $M = 120$  mass univariate models
- **Pretense** again: all elements are unrelated
- **Penalty time** again: permutations?

$$\mathbf{Z}_k^{(m)} = \begin{matrix} & R_1 & R_2 & R_3 & \cdots & R_m \\ R_1 & \left( \begin{array}{c} - \\ z_{21k} \\ z_{31k} \\ \vdots \\ z_{m1k} \end{array} \right. & \begin{array}{c} R_2 \\ - \\ z_{32k} \\ \vdots \\ z_{m2k} \end{array} & \begin{array}{c} R_3 \\ z_{13k} \\ - \\ \vdots \\ z_{m3k} \end{array} & \begin{array}{c} \cdots \\ \cdots \\ \cdots \\ \cdots \\ \cdots \end{array} & \begin{array}{c} R_m \\ z_{1mk} \\ z_{2mk} \\ z_{3mk} \\ \vdots \\ - \end{array} \end{matrix}$$

# Dealing with inter-region data (IRD)

## • Complexities of IRD

- Some of them are unrelated, but others are correlated
- Correlation structure is intricate
- $0 \leq \rho \leq 0.5$
- Can we do a better job than GLMs or dichotomization?
  - **Challenge: How to characterize the complex structure?**



$$P^{(5)} = \begin{matrix} & z_{21} & z_{31} & z_{41} & z_{51} & z_{32} & z_{42} & z_{52} & z_{43} & z_{53} & z_{54} \\ \begin{matrix} z_{21} \\ z_{31} \\ z_{41} \\ z_{51} \\ z_{32} \\ z_{42} \\ z_{52} \\ z_{43} \\ z_{53} \\ z_{54} \end{matrix} & \begin{pmatrix} 1 & \rho & \rho & \rho & \rho & \rho & \rho & 0 & 0 & 0 \\ \rho & 1 & \rho & \rho & \rho & 0 & 0 & \rho & \rho & 0 \\ \rho & \rho & 1 & \rho & 0 & \rho & 0 & \rho & 0 & \rho \\ \rho & \rho & \rho & 1 & 0 & 0 & \rho & 0 & \rho & \rho \\ \rho & \rho & 0 & 0 & 1 & \rho & \rho & \rho & \rho & 0 \\ \rho & 0 & \rho & 0 & \rho & 1 & \rho & \rho & 0 & \rho \\ \rho & 0 & 0 & \rho & \rho & \rho & 1 & 0 & \rho & \rho \\ 0 & \rho & \rho & 0 & \rho & \rho & 0 & 1 & \rho & \rho \\ 0 & \rho & 0 & \rho & \rho & 0 & \rho & \rho & 1 & \rho \\ 0 & 0 & \rho & \rho & 0 & \rho & \rho & \rho & \rho & 1 \end{pmatrix} \end{matrix}$$

# IRD: switching from GLM to LME

- IRD analysis through linear mixed-effects modeling

- One model integrates all ROIs: LME
- ROIs loosely constrained instead of being unrelated
  - Gaussian distribution: Is it far-fetched?
  - Similar to cross-subject variability

- Goal: effects of interest

- Each region pair (RP):  $b_0 + \xi_i + \xi_j$
- Each region:  $b_0 + \xi_i$

- LME wouldn't work!

- *Cul-de-sac!*

Overall effect:  
shared by all ROIs  
and subjects

Effect by  
ith ROI

Effect by  
jth ROI

Effect by  
kth subject

$$z_{ijk} = b_0 + \xi_i + \xi_j + \pi_k + \epsilon_{ijk},$$

$$\xi_i, \xi_j \stackrel{iid}{\sim} \mathcal{N}(0, \lambda^2), \pi_k \stackrel{iid}{\sim} \mathcal{N}(0, \tau^2), \epsilon_{ijk} \sim \mathcal{N}(0, \sigma^2)$$

$$i, j = 1, 2, \dots, m \ (i > j), k = 1, 2, \dots, n,$$

# IRD: one more jump - from LME to **BML**

- **IRD analysis through Bayesian multilevel (BML) modeling**

- **One** model integrates all ROIs: BML (essentially same as LME)

- ROIs loosely constrained

- Gaussian distribution: Is it far-fetched?
- Similar to cross-subject variability

- Goal: effects of interest

- Each **region pair** (RP):  $b_0 + \xi_i + \xi_j$
- Each **region**:  $b_0 + \xi_i$

- LME plus **priors**

- **MCMC**
- Posterior distribution

Overall effect:  
shared by all ROIs  
and subjects

Effect by  
*i*th ROI

Effect by  
*j*th ROI

Effect by  
*k*th subject

$$z_{ijk} | b_0, \xi_i, \xi_j, \pi_k \sim \mathcal{N}(b_0 + \xi_i + \xi_j + \pi_k, \sigma^2),$$

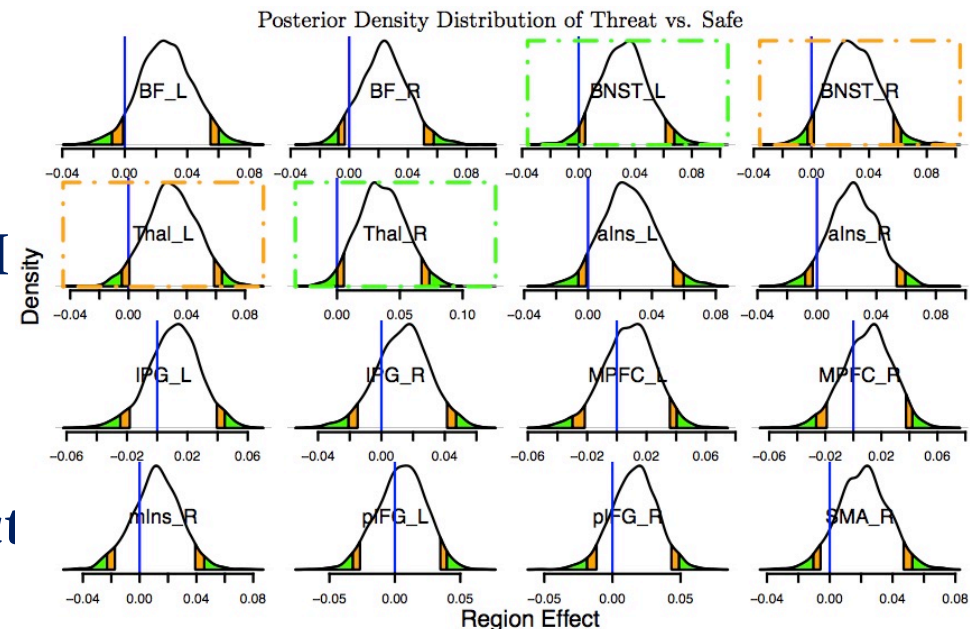
- **Ka-ching!**

$$\xi_i \stackrel{iid}{\sim} \mathcal{N}(0, \lambda^2), \xi_j \stackrel{iid}{\sim} \mathcal{N}(0, \lambda^2), \pi_k \stackrel{iid}{\sim} \mathcal{N}(0, \tau^2)$$

$$i, j = 1, 2, \dots, m \ (i > j), k = 1, 2, \dots, n.$$

# IRD – ROI effect from BML: **full distributions**

- ROI-based BML: **16 ROIs**
- **Full report** with richer information: posterior distributions for each ROI
  - No dichotomization
  - **Nothing hidden under sea level**
- **4 ROIs** with strong evidence of effect compared to
  - Region effect inferences: unavailable from GLM and graph theory
  - **Hubness?**

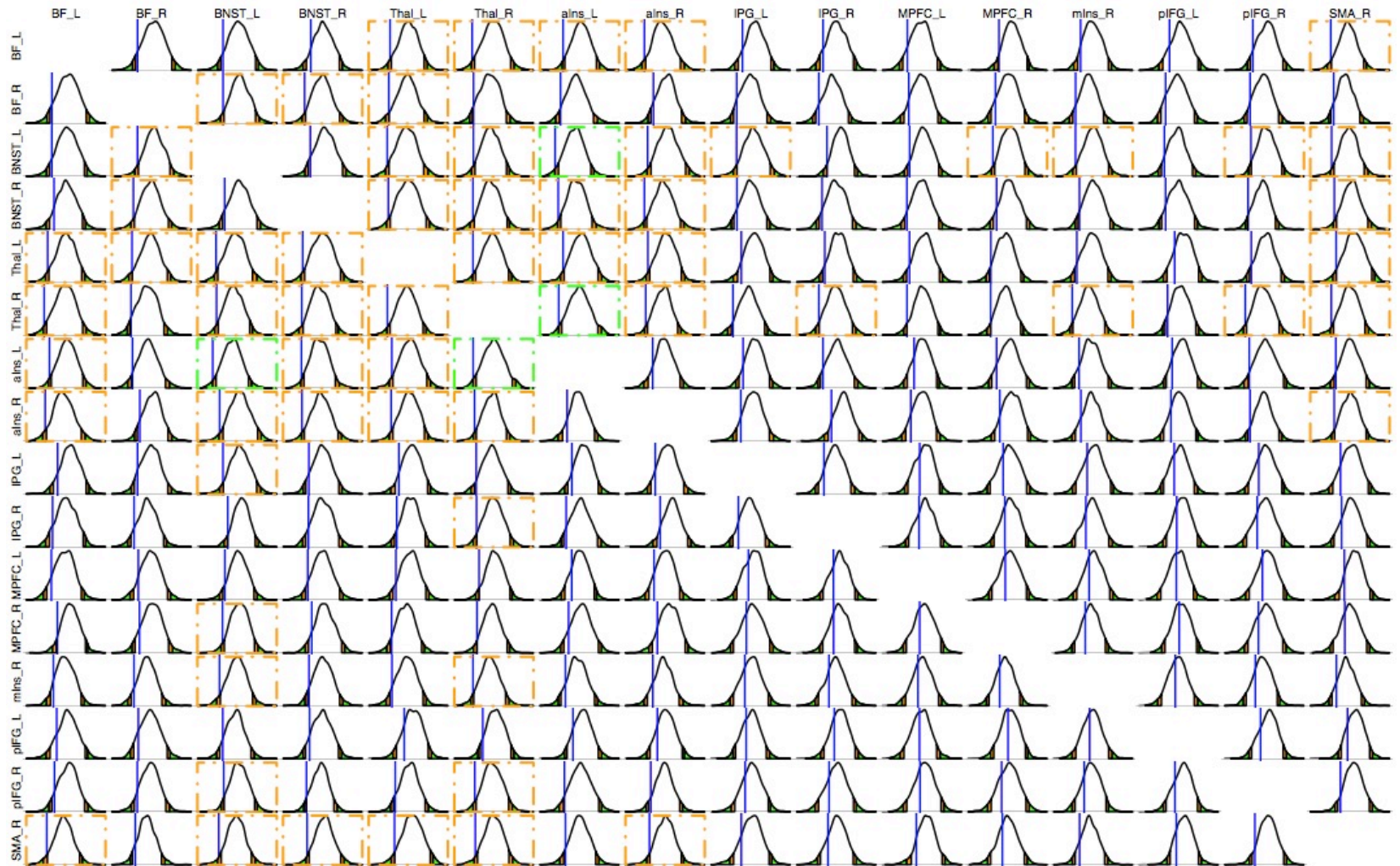


## IRD– ROI effect from BML: **quantile interval**

- ROI-based BML: 16 ROIs
- full report with quantile intervals
- **4 ROIs** with strong evidence for region effect

ROI	mean	std err	2.5%	5%	50%	95%	97.5%
BF_L	0.026	0.017	-0.008	-0.001	0.026	0.055	0.060
BF_R	0.024	0.016	-0.007	-0.003	0.024	0.051	0.057
<b>BNST_L</b>	<b>0.032</b>	<b>0.017</b>	<b>0.001</b>	<b>0.005</b>	<b>0.032</b>	<b>0.061</b>	<b>0.067</b>
BNST_R	0.029	0.017	-0.002	0.002	0.028	0.057	0.062
Thal_L	0.030	0.017	-0.004	0.001	0.029	0.059	0.064
<b>Thal_R</b>	<b>0.036</b>	<b>0.019</b>	<b>0.000</b>	<b>0.006</b>	<b>0.035</b>	<b>0.067</b>	<b>0.073</b>
aIns_L	0.025	0.017	-0.006	-0.001	0.025	0.053	0.060
aIns_R	0.025	0.017	-0.008	-0.003	0.025	0.054	0.059
IPG_L	0.011	0.017	-0.024	-0.018	0.012	0.039	0.045
IPG_R	0.014	0.017	-0.021	-0.015	0.014	0.041	0.047
MPFC_L	0.008	0.017	-0.030	-0.021	0.009	0.036	0.040
MPFC_R	0.010	0.017	-0.026	-0.019	0.011	0.038	0.042
mIns_R	0.012	0.017	-0.023	-0.017	0.012	0.039	0.045
pIFG_L	0.005	0.019	-0.032	-0.026	0.006	0.035	0.039
pIFG_R	0.016	0.017	-0.018	-0.011	0.017	0.043	0.049
SMA_R	0.021	0.016	-0.010	-0.006	0.021	0.047	0.052

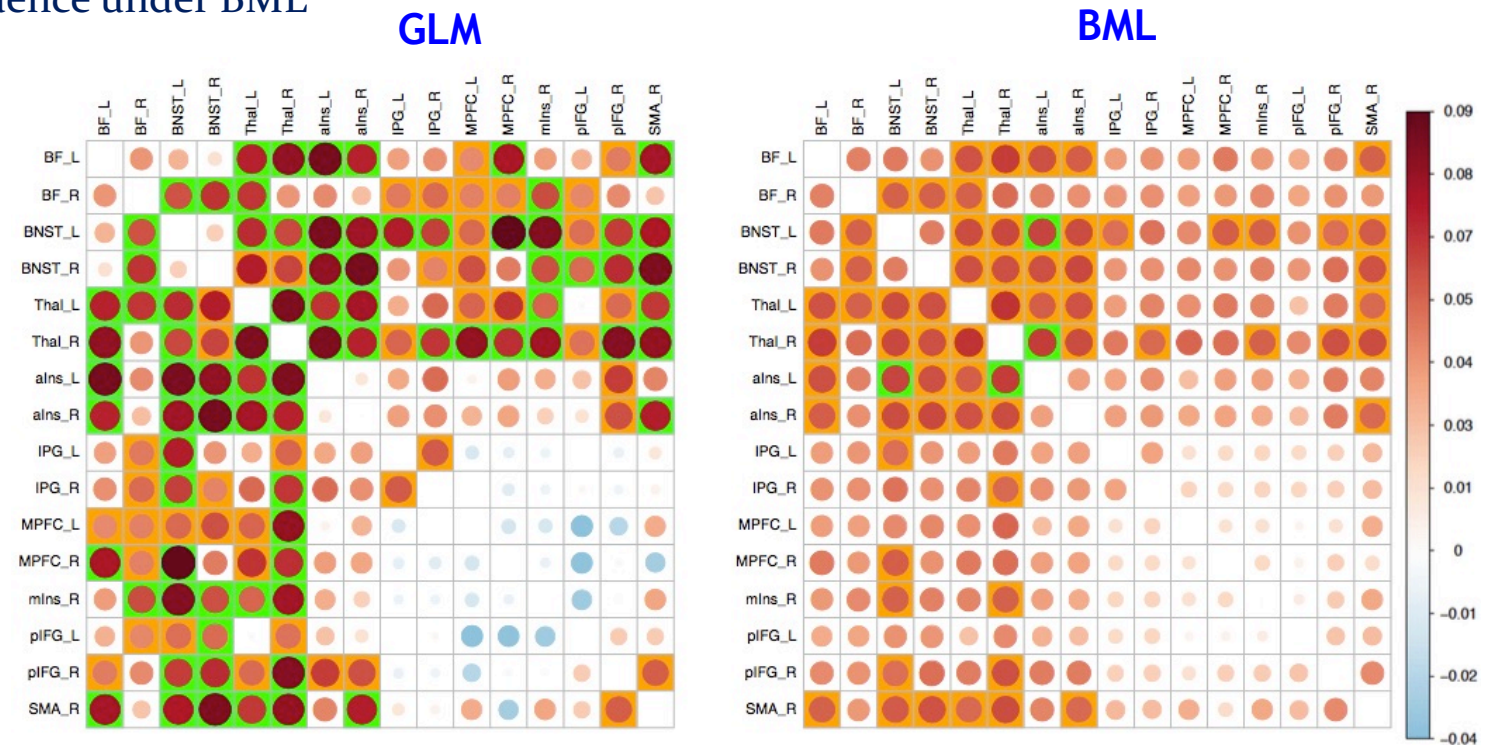
# IRD – RP effect from BML: full distributions





# IRD- RP effect from BML

- ROI-based BML: 16 ROIs
- full report for all region pairs (RPs)
- Comparisons with GLMs: **nothing hidden under sea level**
  - 63 RPs identified by GLMs with  $p$  of 0.05: **none survived** after correction with NBS via permutations
  - **33 RPs** with strong evidence under BML



# BML: model validations

- ROI-based BML with IRD of 16

## ROIs: cross-validation

- Leave-one-out information criterion (LOOIC)

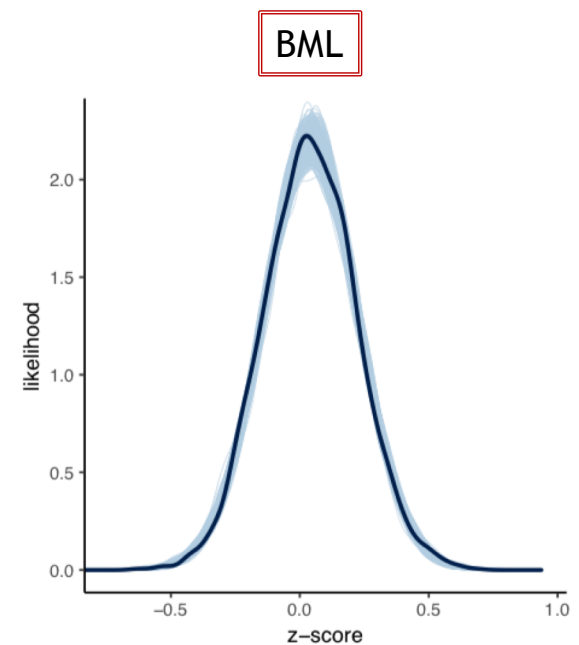
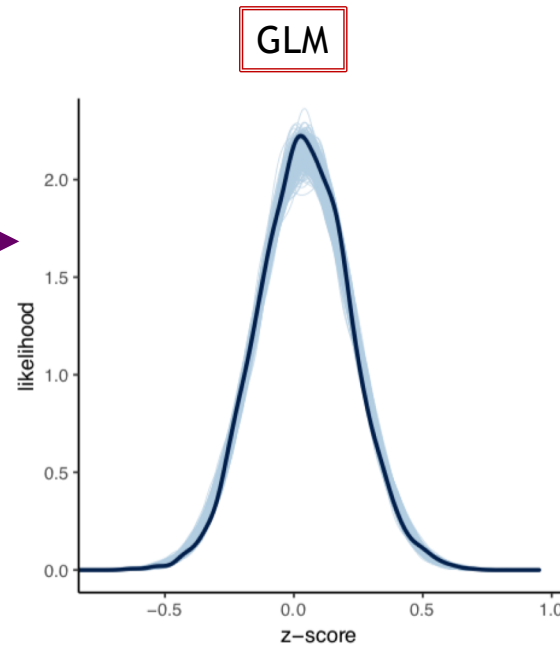
### Cross-validation

Model	LOOIC	SE
GLM	-2808.31	101.65
BML0	-4543.77	102.97

- Posterior predictive checking

## • Effects of BML

- Regularizing ROIs: don't fully trust individual ROI data
- Sacrificing fit at each ROI; achieving better overall fit



# Summary

- **Efficient modeling through information pooling**
  - How to effectively avoid multiplicity penalty?
- **Demo dataset #1**
  - Resting state: seed-based correlation analysis
  - Handling multiple testing through **ROI-based group analysis**
    - How to avoid penalty of modeling across voxels or ROIs?
  - **Program available** in AFNI: **BayesianGroupAna.py**
- **Demo dataset #2**
  - Group analysis with correlation matrices among ROIs
  - Handling multiple testing for **inter-region data (IRD) analysis**
    - How to avoid penalty of modeling across voxels or ROIs?
  - More applications
    - **DTI data: white matter connectivity network**
    - **Naturalistic data analysis (1:20PM, Sept. 25)**

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