# Do We Have to Deal with Multiple Comparisons in Neuroimaging?


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afni26_ROI-based-modeling.pdf




# Preview

- **Multiplicity problems in neuroimaging**
- **Improving modeling from two perspectives**
  - Weirdness of *p*-value
  - Information waste and inefficient modeling
- **Application #1: region-based analysis (RBA)**
  - Whole-brain voxel-wise group analysis

  Program available in AFNI: ***BayesianGroupAna.py***
- **Application #2: matrix-based analysis (MBA)**
  - FMRI: inter-region correlation (IRC)
  - DTI: white-matter properties (FA, MD, RD, AD, etc.)
  - Naturalistic scanning: Inter-subject correlation (ISC)

  Program available in AFNI: ***MBA***

# Conventional group analysis: voxel-wise

- **Simple situations**
  - Student's *t*-test: one-, two-sample, paired *t*-test
  - General linear model (GLM) with between-subjects variables (sex, age, ...)
  - **3dttest++** and **3dMVM** in AFNI
- **Situations with within-subject factors**
  - Univariate GLM for AN(C)OVA: **not always performed correctly**
  - Multivariate GLM: **3dMVM** in AFNI
- **Other complicated situations**
  - Missing data, within-subject quantitative covariates (reaction time, ...)
  - Linear mixed-effects modeling: **3dLME** in AFNI
- **Headache: multiplicity!**

# Conventional matrix-based analysis

- **Matrices from individual subjects**
  - Inter-region correlations (IRCs), inter-subject correction (ISC)
  - White-matter properties: missing data
  - Others: coherence, mutual information, entropy, …
- **Group analysis**
  - Mirroring adoption of whole-brain analysis
  - Univariate GLM: **treating matrix elements as isolated entities**
  - NBS, CONN, FSLNets in FSL, GIFT, Brain Connectivity Toolbox, …
- **Graph theory**
  - Arbitrary thresholding, artificial dichotomization
  - Garden of forking paths: scores of metrics (hub, community, clique, small-world, …)
- **Headache: multiplicity!**

# 4 multiplicity problems

- **Element-wise modeling (multi-model problem)**
  - aka massively univariate modeling
  - Perform whole-brain voxel-wise or element-wise in matrix analysis
  - Pretend all spatial elements are isolated and unrelated to each other
  - Recoup the false assumption through correction: heavy penalty and inefficient
- **Sidedness testing**
  - Simultaneously infer both positive and negative effects: dominantly adopted
- **Multiple comparisons (conventional concept)**
  - Simultaneously compare groups, conditions, and interactions
  - Not much attention paid so far
- **Multiverse problem:** researcher degrees of freedom
  - Thousands of options coexist: different preprocessing pipelines, modeling strategies, software
  - Garden of forking paths: only reporting "significant discoveries"
  - No easy solutions exist

# Conventional statistical testing strategy

- **Null hypothesis significance testing (NHST)**
  - We are all indoctrinated under the paradigm
  - Build a strawman $H_0$: nothing happens in brain
  - Attack strawman $H_0$ with weirdness of data under $H_0$ : ***p*-value**
    - **Type I error** = P(reject $H_0$ | $H_0$) = false positive = *p*-value
    - **Type II error** = P(accept $H_0$ | $H_1$) = false negative
  - Dichotomize data based on magic number **0.05**
- **Nice properties of NHST**
  - **Consistent with Karl Popper's philosophy**
    - **Falsification or refutation**
    - **Inductive: all swans are white**
  - **Intuitive: innocent until proven guilty**
  - **Economical/utility: categorization**
    - **ADHD, autism, emission test (pass vs fail), …**

**Courtroom**

Hidden Truth

| | Innocent | Guilty |
|---|---|---|
| Reject $H_0$ (guilty) | Type I Error (defendant very unhappy) | Correct |
| Fail to Reject $H_0$ (not guilty) | Correct | Type II Error (defendant very happy) |

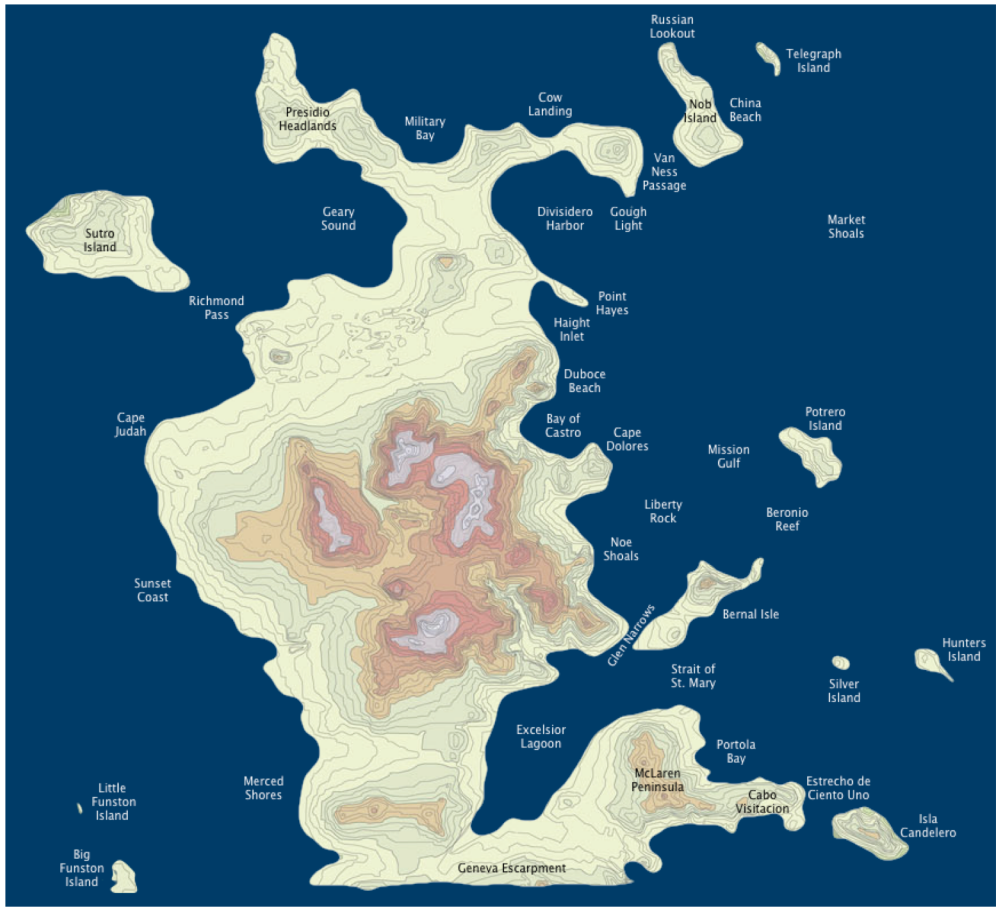
# Weirdness of *p*-value

- **Strawman $H_0$: artificial construct**
  - Witch hunt: usually of no interest
    - Effect of absolute zeros? Who believes no effect everywhere in brain?
  - Artificially binarize continuous world: innocent vs guilty
    - "activated" vs "not activated"? Or strength of evidence for activation?
  - ***P*-value flows in our blood: unaware of weirdness and troubles**
  - Disconnection/misinterpretation: $P(\text{weirdness} \mid H_0) \neq P(H_0 \mid \text{data})$
    - ***P*-value:** $P(\text{weirdness} \mid H_0)$
    - Research interest: $P(\text{effect} > 0 \text{ or } < 0 \mid \text{data})$

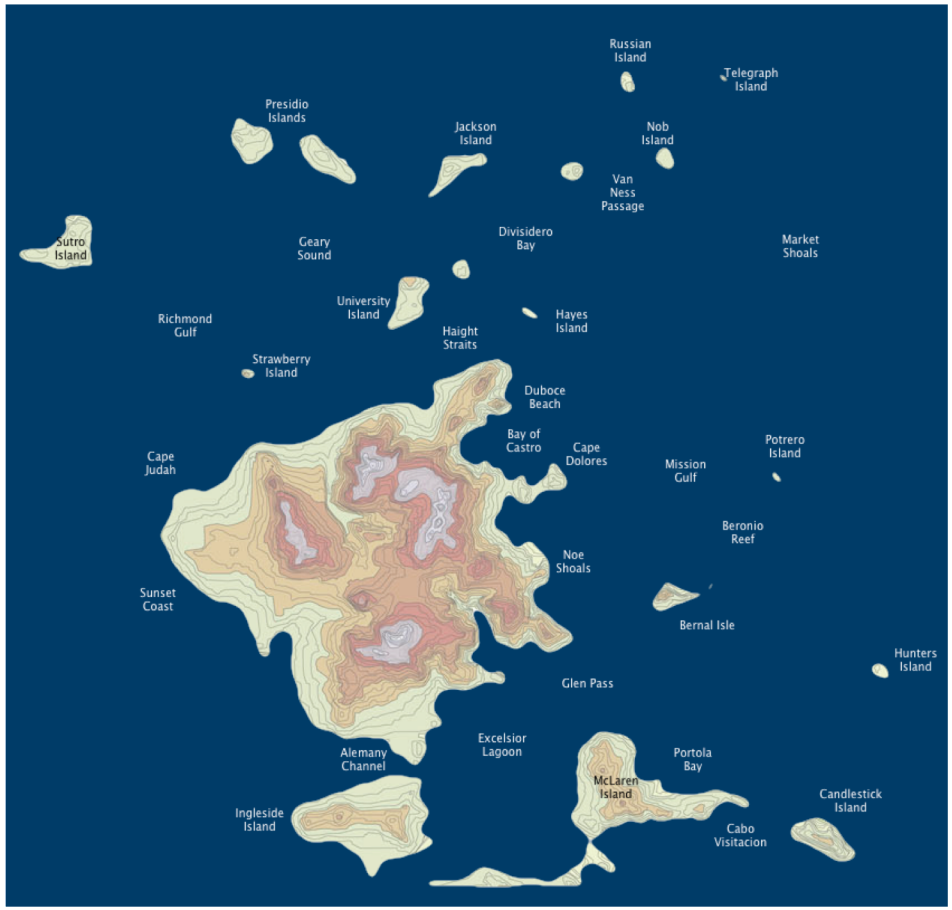
- **Problems with dichotomous decision**
  - *P*-value of 0.05 vs 0.055 or cluster of 54 vs 53 voxels?
  - Statistically insignificant = non-existing effect? Absence of evidence = evidence of absence?
  - Difference between "significant" & "insignificant" results: not necessarily significant
  - Selection bias about effect estimates in results reporting
    - Power analysis based on literature: not very useful other than pleasing grant reviewers
    - One source of reproducibility problems: big/tall parents (violent men, engineers) have more sons; beautiful parents (nurses) have more daughters; power posing
    - Unreliable meta analyses: many potential effects unreported

# Clusters vs islands: arbitrariness

## Threshold (sea level) 1




## Threshold (sea level) 2



# Problems with clusters

- **Cluster thresholding: "islands above sea level" approach**
  - Use cluster size as leverage in controlling overall false positives (FWE)
    - Monte Carlo simulations, RFT, combination of cluster size and signal strength
  - Hide everything below threshold
    - Arbitrary: regardless of rigor in FWE controllability
  - Penalize and discriminate small regions
    - Unfair: 2 regions with same signal strength: one large and one small
    - 2 regions with same signal strength: one distant and one contiguous
  - Clusters are statistically defined
    - Do not respect anatomical structures
    - Lack spatial specificity: bleeding effect or forming huge clusters
    - Focus on statistically defined "peak" voxels
  - Sidedness for whole brain: one- or two-sided?

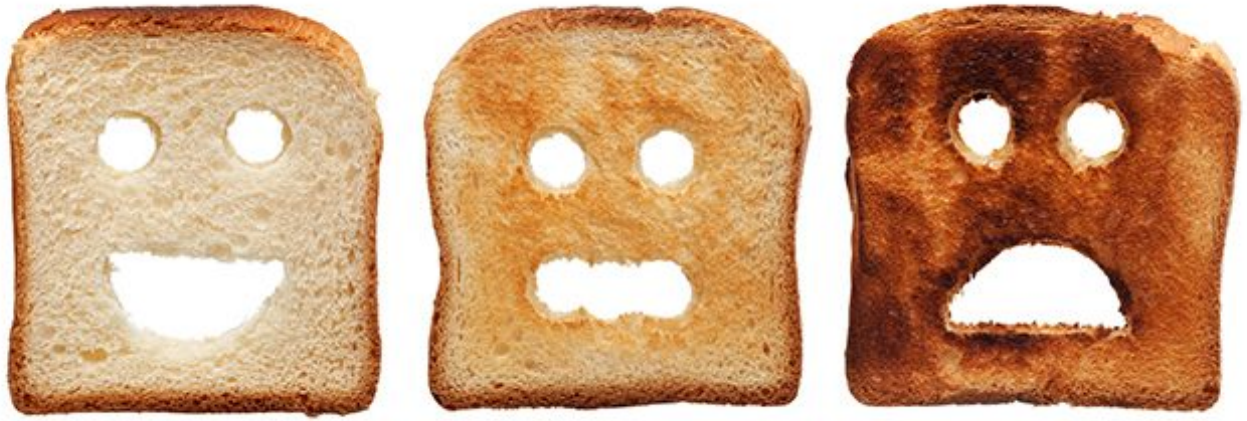
# Problems with element-wise modeling

- **First step: apply same model to all elements**
  - Pretend all elements are isolated and unrelated: **false assumption**
  - Source of multi-model problem: number of models = number of elements
- **Second step: correct for multi-model and false assumption**
  - Use cluster size as leverage in controlling overall false positives
    - Monte Carlo simulations, RFT, combination of cluster size and signal strength
- **Problems**
  - Loss of efficiency due to split-modeling and false assumption
  - Over-penalization
  - Reinforcing arbitrary thresholding and dichotomization
- **How can we do better?** Prior knowledge: elements are not unrelated
- **Conceptually $P(\text{weirdness}|\ H_0) \neq P(H_0|\text{data})$, but practically $P(\text{weirdness}|\ H_0) \cong P(H_0|\text{data})$?**

# How to incorporate prior knowledge?

- **Priors are omnipresent in life**
  - Walking stairs, prejudices, stereotypes, etc.
- **But priors are not always easy to digest!**
  - **Infamy: subjective???**
  - Are we eating acrylamide for breakfast?

$$\pi(\theta \mid y) = \frac{\pi(y \mid \theta)\pi(\theta)}{\pi(y)}$$



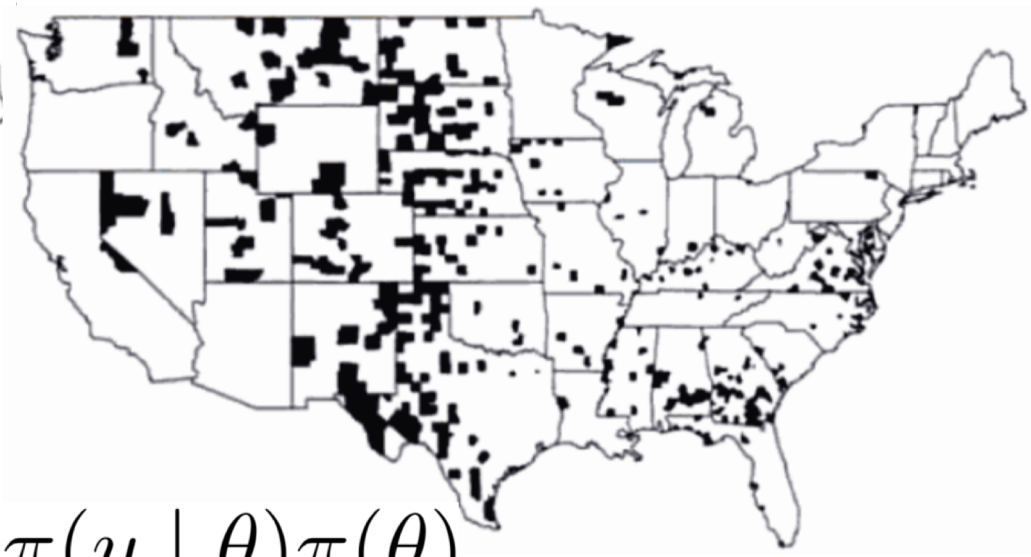
Both sides good  One side BURNT  Both sides BURNT

# How to incorporate prior knowledge?

- **Kidney cancer distribution among U. S. counties**

Highest rate

lowest rate



**Calibration**

$$\pi(\theta \mid y) = \frac{\pi(y \mid \theta)\pi(\theta)}{\pi(y)}$$

# How to incorporate prior knowledge?

- **More examples**
  - LeBron James field goals percentage: 50.4%
  - Monthly divorce rate, suicide rate
  - …
- **KISS principle**
- **Stein's paradox (1956)**

**Calibration**

$$\pi(\theta \mid y) = \frac{\pi(y \mid \theta)\pi(\theta)}{\pi(y)}$$

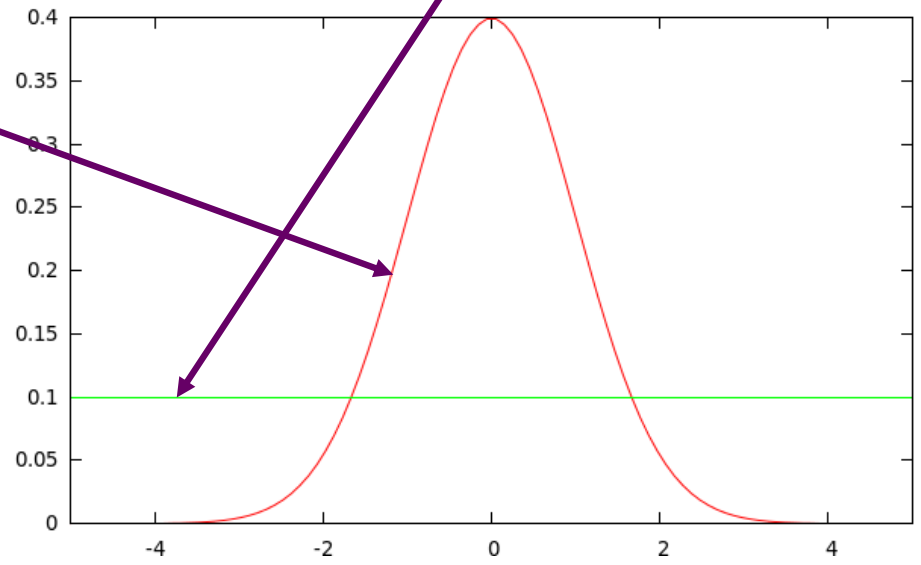
- **Free market vs regulations**

# Morals from kidney cancer data

- **Multiplicity problem: > 3000 counties!**
  - Divide *p*-value by number of counties?
  - Borrow idea from neuroimaging: leverage geographical relatedness?
- **What can we learn from the example? Food for thought**
  - Care about the strawman $H_0$ (zero kidney rate), false positives, *p*-value?
  - Trust individual county-wise estimates? Unbiased! **BLUE**
    - **Incorrect sign errors** (type S): some counties really have higher kidney cancer rate than others?
    - **Incorrect magnitude** (type M): some counties really have higher/lower cancer rate?
  - Would correction for multiplicity help at all?
    - Useless in controlling for type S and M errors
- **How can we do better?**
  - Information across spatial elements can be shared and regularized
  - **How???**

# What do we know about spatial elements?

- **Element-wise modeling**
  - Pretend full ignorance: fully trust the data
  - Uniform distribution: each element equally likely to have any value in (- ∞, +∞)
  - Similar for variances: variances can be negative in ANOVA
- **One crucial prior for spatial elements**
  - Reasonable to assume Gaussian distribution?
  - Gaussian assumption adopted everywhere!
    - Subjects, residuals across TRs
  - How can Gaussian assumption help?
    - Loosely constraining elements
    - No full trust for individual estimates
    - Information sharing: shrinkage or partial pooling
    - Controlling type S and M errors



# Short summary: what we intend to achieve

- **Abandon strawman and *p*-value**
  - Directly focus on research interest $P(\text{effect} > 0 \mid \text{data})$
- **Build one model**
  - Incorporate all elements into a multilevel or hierarchical structure
  - Loosely constrain elements: leverage **prior knowledge**
  - Achieve higher modeling efficiency: **no more multiplicity**!
  - Validate the model by comparing with potential competitors
  - Be conservative on effect estimates by controlling type S and M errors: **biased?**
  - Always be mindful of uncertainties: strength of evidence (no proof)
- **Avoid dichotomous decisions**
  - Report full results if possible
  - Highlight instead of hide based on gradient of evidence

# Application #1: region-based analysis

- **Dataset**
  - Subjects: $n$ = 124 children; resting-state data (Xiao et al., 2019)
  - 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-wise group analysis: GLMs**
  - Focus: association between $x$ and seed-based correlation ($z$-score)
  - Pretense: voxels unrelated - equal likelihood within $(-\infty, \infty)$
  - Information waste!
  - GLMs: mass univariate - multiplicity

  $m$ = 100,000 voxels → 100,000 models

Uniform distribution: total freedom - each parameter on its own

$$\begin{aligned} \text{1st voxel:} \quad & z_1 = a_1 + b_1 x + \epsilon_1 \\ \text{2nd voxel:} \quad & z_2 = a_2 + b_2 x + \epsilon_2 \\ & \dots \\ m\text{th voxel:} \quad & z_m = a_m + b_m x + \epsilon_m \end{aligned}$$

Xiao et al., 2019. Neuroimage 184:707-716

# GLMs: dealing with multiplicity!

- **Voxel-based 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: still GLMs

- **Region-wise analysis : GLMs**
  - Focus: association between and seed-based correlation ($z$-score)
  - Pretense: ROIs unrelated
  - GLMs: mass univariate

    $m$ = 21 ROIs → 21 models
  - Penalty time for pretense: multiple testing – what to do?
    - Bonferroni? Unbearable
    - What else?

Uniform distribution: total freedom - each parameter on its own.

$$\begin{aligned}
\text{1st ROI: } \boldsymbol{z}_1 &= a_1 + b_1\boldsymbol{x} + \boldsymbol{\epsilon}_1 \\
\text{2nd ROI: } \boldsymbol{z}_1 &= a_2 + b_2\boldsymbol{x} + \boldsymbol{\epsilon}_2 \\
&\dots \\
m\text{th ROI: } \boldsymbol{z}_m &= a_m + b_m\boldsymbol{x} + \boldsymbol{\epsilon}_m
\end{aligned}$$

# Switching from GLMs to LME

- **Region-wise analysis : Linear Mixed-Effects (LME) model**
  - One model integrates all regions
  - ROIs loosely constrained instead of being unrelated
    - Gaussian distribution: Is it far-fetched or subjective?
    - Similar to cross-subject variability
  - Goal: effect of interest $b + \beta_j$
  - Differentiation: fixed vs. random
    - Fixed: **epistemic** uncertainty
    - Random: **aleatoric** uncertainty
  - What can we get out of LME?
    - Conventional framework
    - Estimates for fixed effects
    - Variances for random effects
  - ***Dead end!***

New components

idiosyncratic effect of *i*th subject

Overall effect: shared by all ROIs and subjects

Unique effect of *j*th ROI

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

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

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

# Switching from GLMs to BML

- **Region-wise analysis : Bayesian multilevel (BML) model**
  - One model integrates all regions: basically same as LME
  - ROIs loosely constrained instead of being unrelated
    - Gaussian distribution: Is it far-fetched or subjective?
    - Similar to cross-subject variability
  - Goal: effect of interest $b + \beta_j$
  - No more differentiation: fixed vs. random
    - All parameters: aleatoric
  - Same model as LME plus priors
    - Markov chain Monte Carlo (MCMC)
    - Inferences via posterior distribution
  - *Ka-ching!*

New components

Idiosyncratic effect by *i*th subject

Overall effect: shared by all ROIs and subjects

Unique effect by *j*th ROI

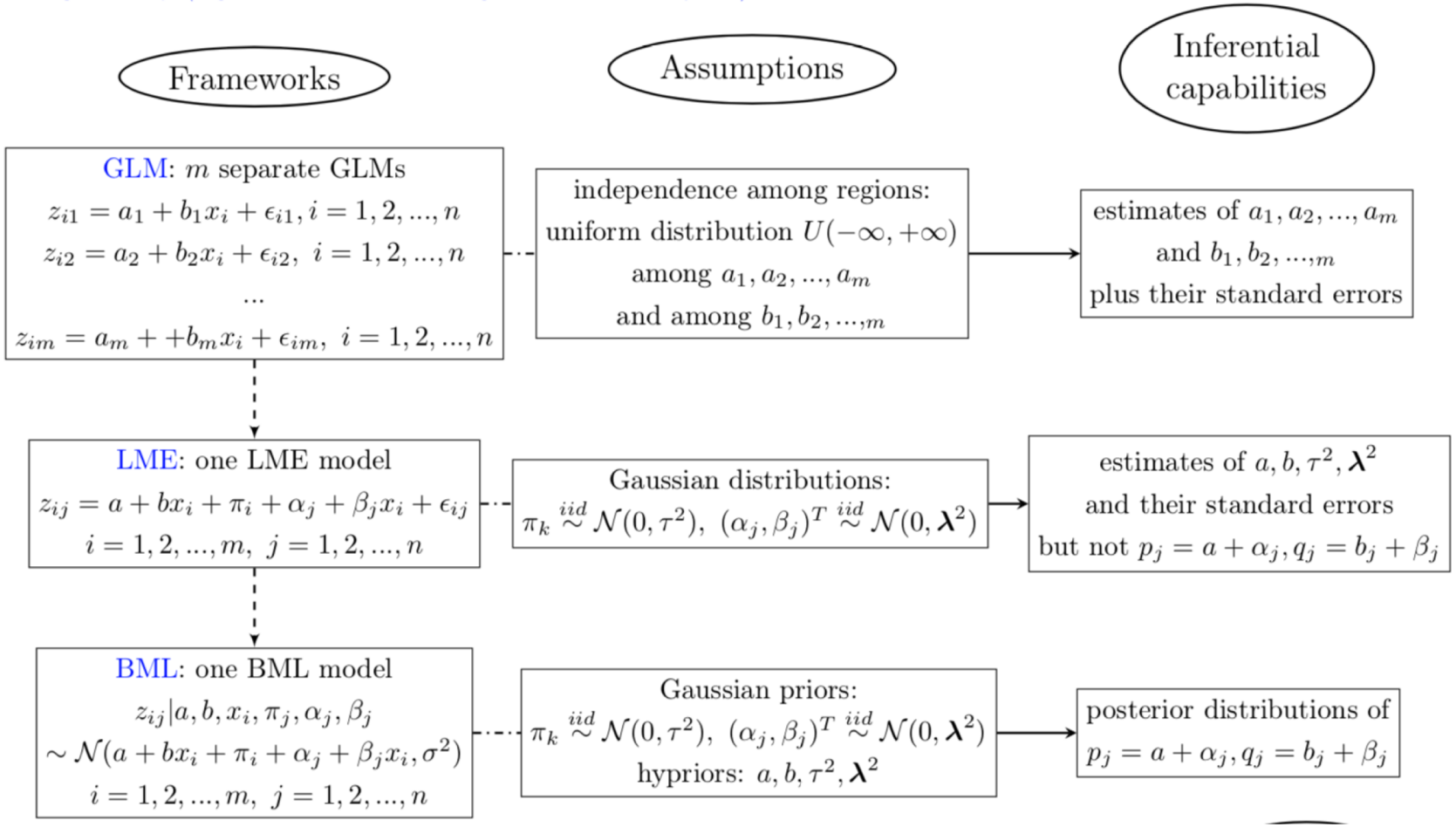
$$z_{ij} = a + bx_i + \pi_i + \alpha_j + \beta_j x_i + \epsilon_{ij}$$

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

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

Chen, et al, 2019. Handling Multiplicity in Neuroimaging through Bayesian Lenses with Multilevel Modeling. Neuroinformatics.

# From GLMs to LME to BML




Chen, et al, 2019. Handling Multiplicity in Neuroimaging through Bayesian Lenses with Multilevel Modeling. Neuroinformatics.

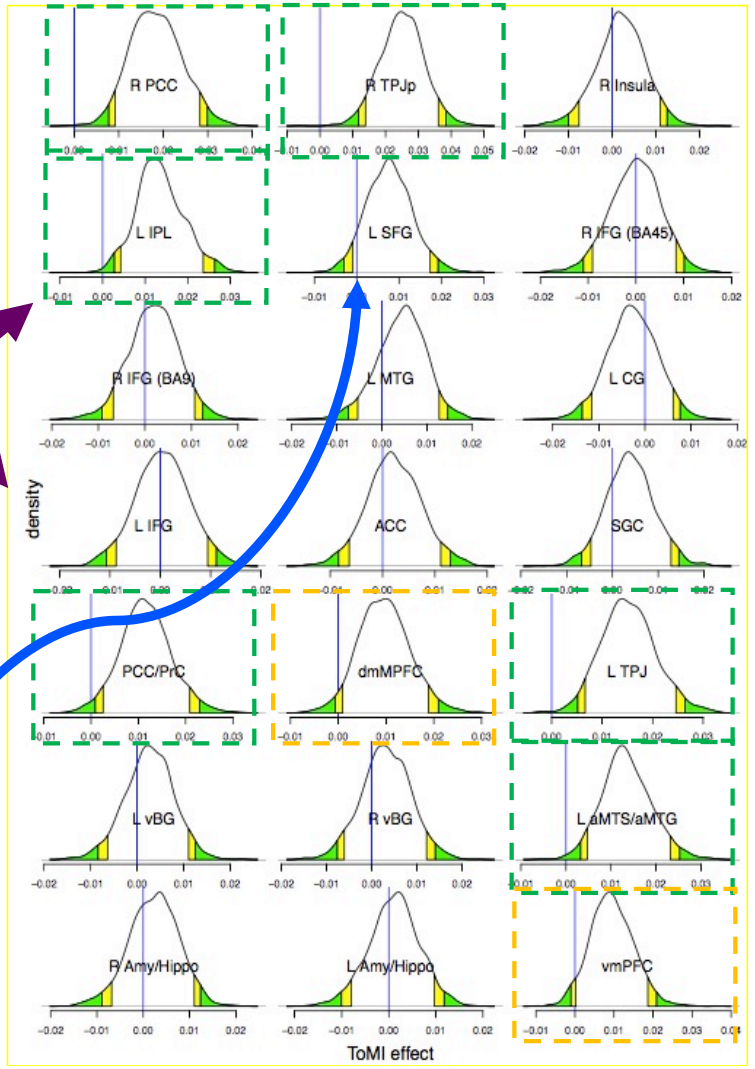
# Inferences from BML: full distributions

- **Region-based BML: 21 ROIs**
- **Full report with richer information: posterior distributions for each ROI**
  - No dichotomization
  - No results hiding
  - No discrimination against small regions
  - No ambiguities about spatial specificity
  - No inconvenient interpretation of confidence interval
  - **Evidence for each ROI**: $P(\text{effect} > 0 \mid \text{data})$

Highlight, not hide

- **8 ROIs with strong evidence of effect compared to**
  - Region-wise GLM with Bonferroni correction
  - Voxel-wise GLM at cluster level: 4 clusters

How about Left SFG?



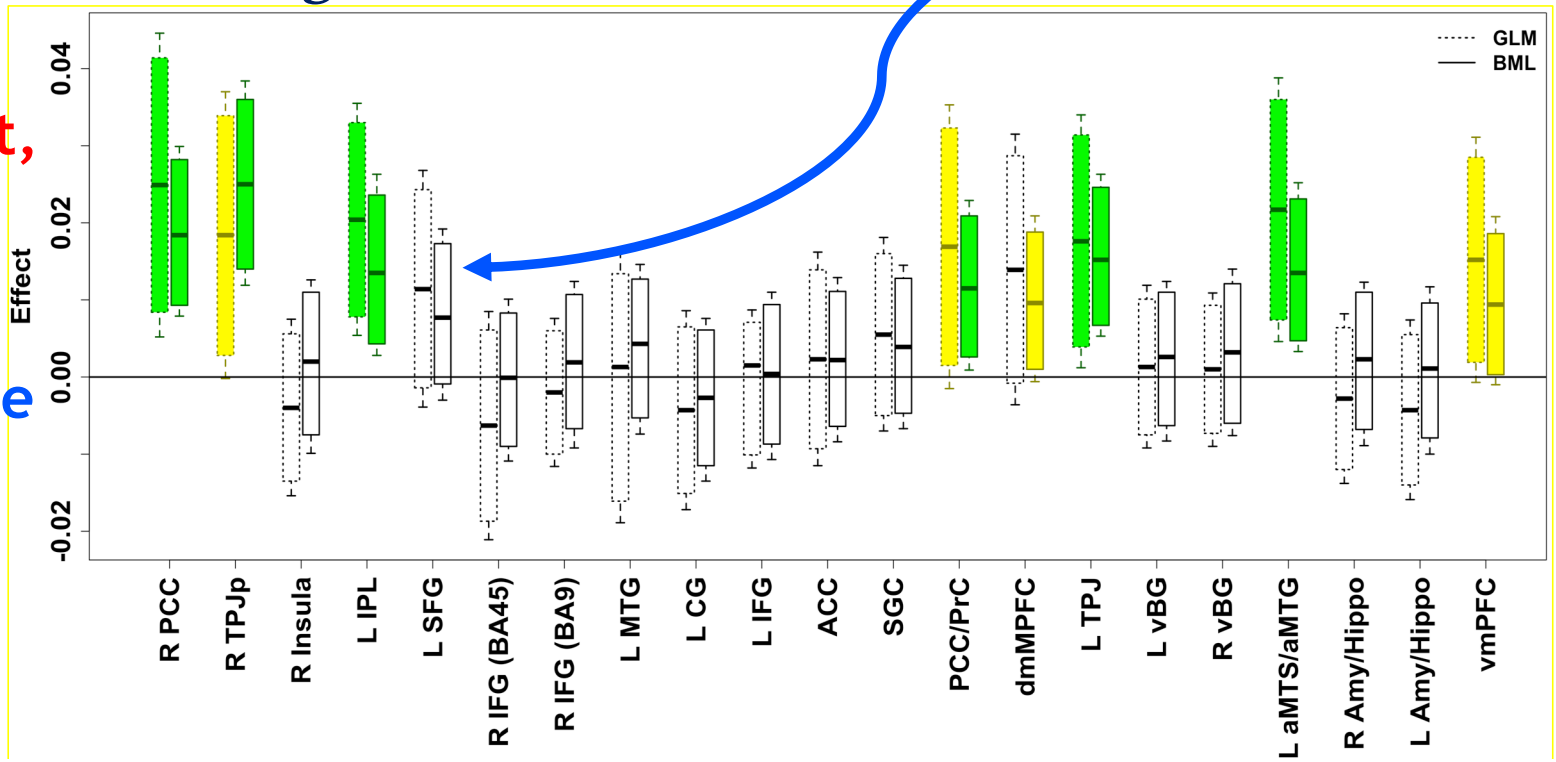
# Inferences from BML: uncertainty

- ROI-based BML: 21 ROIs
- Full report with bar graph uncertainty intervals
  - Nothing hidden under sea level
- 8 ROIs with strong evidence for effect of interest

How about Left SFG?

Highlight, not hide

Shrinkage / partial pooling



# BML: model validations

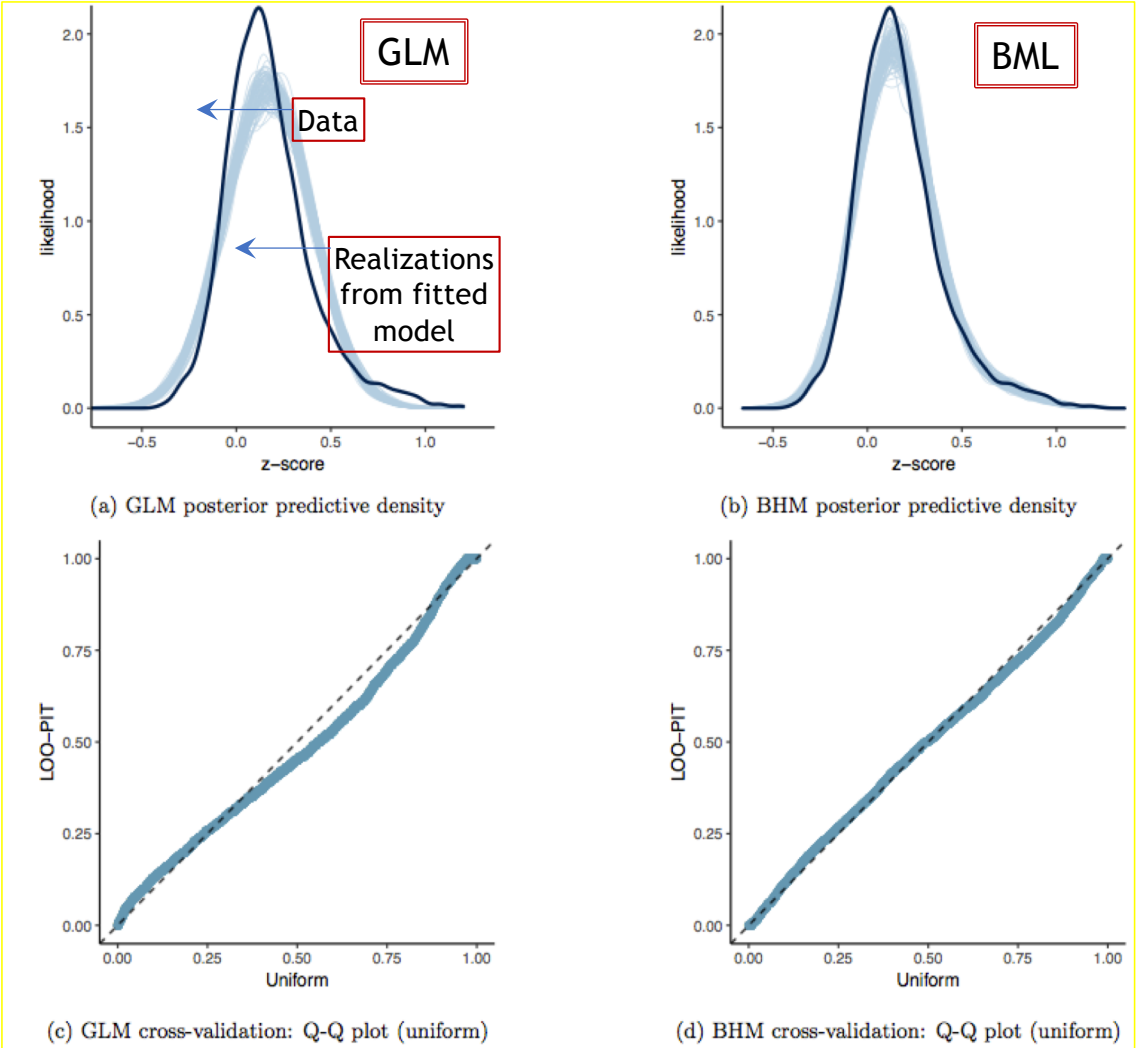
- **ROI-based BML with 21 ROIs: cross-validation**
  - Leave-one-out information criterion (LOOIC)

**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




(a) GLM posterior predictive density

(b) BHM posterior predictive density

(c) GLM cross-validation: Q-Q plot (uniform)

(d) BHM cross-validation: Q-Q plot (uniform)

# BML: Whole-brain vs. region-base analysis

- **Region-based analysis**
  + high region specificity: region definitions considered as priors
  + low computational cost
  + avoiding potential alignment issues by defining regions in native space
  - not all regions have been defined
  - information loss due to averaging within each region
  - region definitions can be tricky
    - relying on results accuracy in literature (e.g., publication bias)
    - different atlases/parcellations
- **Whole-brain analysis**
  + independent of region definitions
  + less likely to miss small regions that are not in available atlases/parcellations
  - vulnerable to poor alignment across subjects
  - region specificity problem
    - Voxel-wise results do not respect region definitions
  - Computationally challenging
    - hopeful: within-chain parallelization and GPU usage

# Application #2: matrix-based analysis

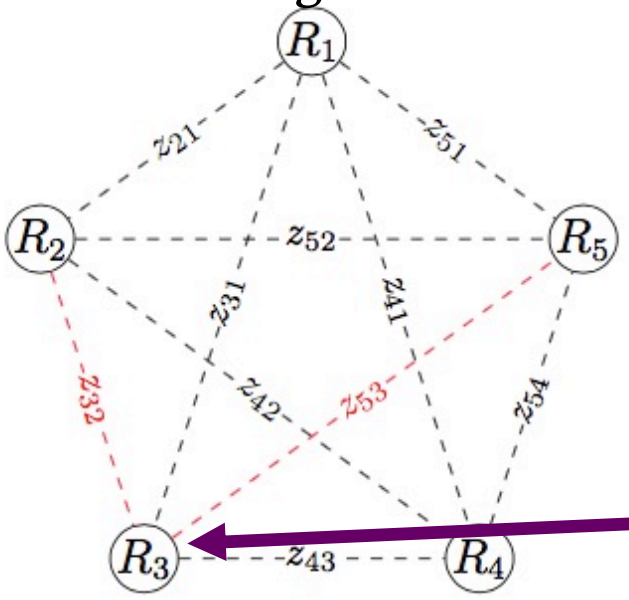
- **Dataset: correlation matrix**
  - Subjects: $n$ = 41 subjects; response-conflict task (Choi et al., 2012)
  - Individual subjects: correlation matrix among $m$ = 16 ROIs
  - How to go about group analysis?
    - **GLM for each element in correlation matrix: NBS, CONN, FSLNets in FSL, GIFT**
    - **Binarization approach: graph theory**
  - More broadly: matrix-based analysis (MBA) ("network modeling")
    - **Inter-region correlation (IRC): FMRI**
    - **White matter properties (FA, MD, ...): DTI**
    - **Other matrices (e.g., coherence, entropy, mutual information)**
- **Focus on GLM**
  - Student $t$-test or GLM on each element
    - $M$ = 120 massively univariate models
  - Pretense again: all elements are unrelated
  - Equal likelihood within $(-\infty, \infty)$
  - Information waste
  - Penalty time again: permutations? FDR?

$$\boldsymbol{Z}_k^{(m)} = \begin{array}{c} \\ R_1 \\ R_2 \\ R_3 \\ \vdots \\ R_m \end{array} \begin{array}{c} \begin{array}{cccccc} R_1 & R_2 & R_3 & \cdots & R_m \end{array} \\ \begin{pmatrix} - & z_{12k} & z_{13k} & \cdots & z_{1mk} \\ z_{21k} & - & z_{23k} & \cdots & z_{2mk} \\ z_{31k} & z_{32k} & - & \cdots & z_{3mk} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ z_{m1k} & z_{m2k} & z_{m3k} & \cdots & - \end{pmatrix} \end{array}$$

Choi et al., 2012. Neuroimage 59(2):1912-1923

# Dealing with inter-region correlations (IRCs)

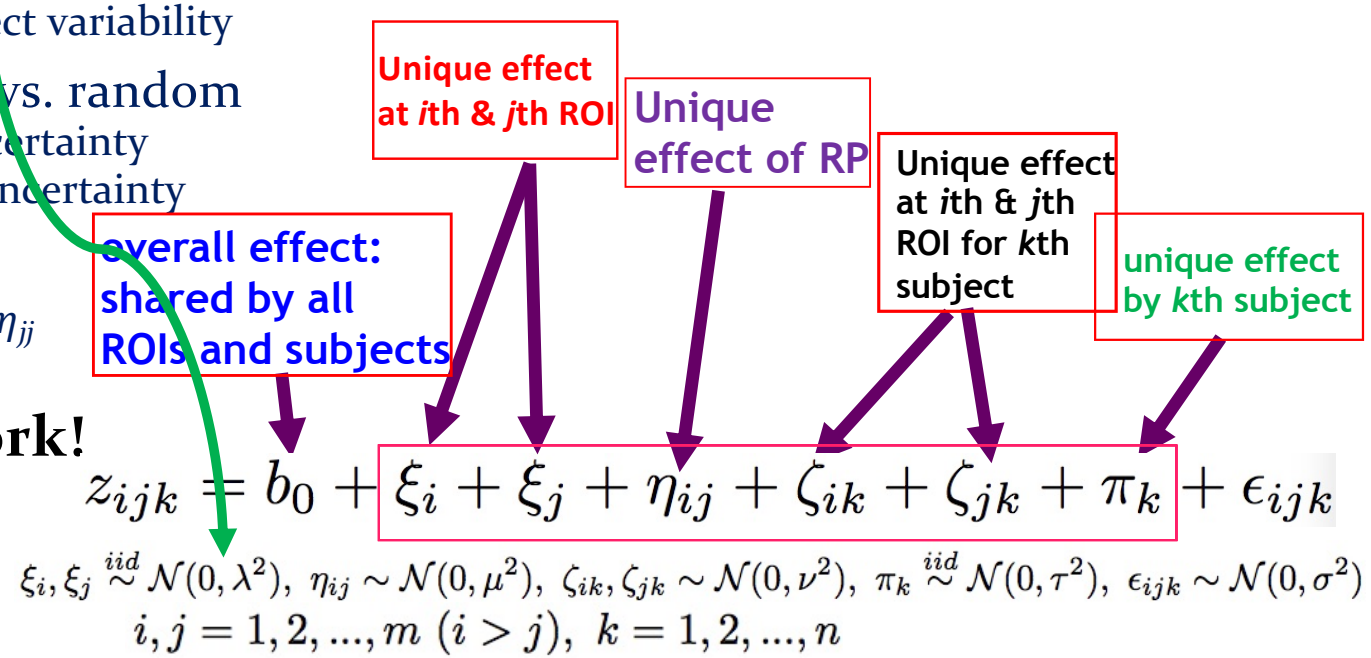
- **Complexities of IRCs**
  - Some region pairs are unrelated, but others are correlated
  - Correlation structure is intricate
  - $0 \leq \rho \leq 0.5$
  - Can we do a better job than GLMs or dichotomization?
    - **Challenge: How to characterize the complex structure?**




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

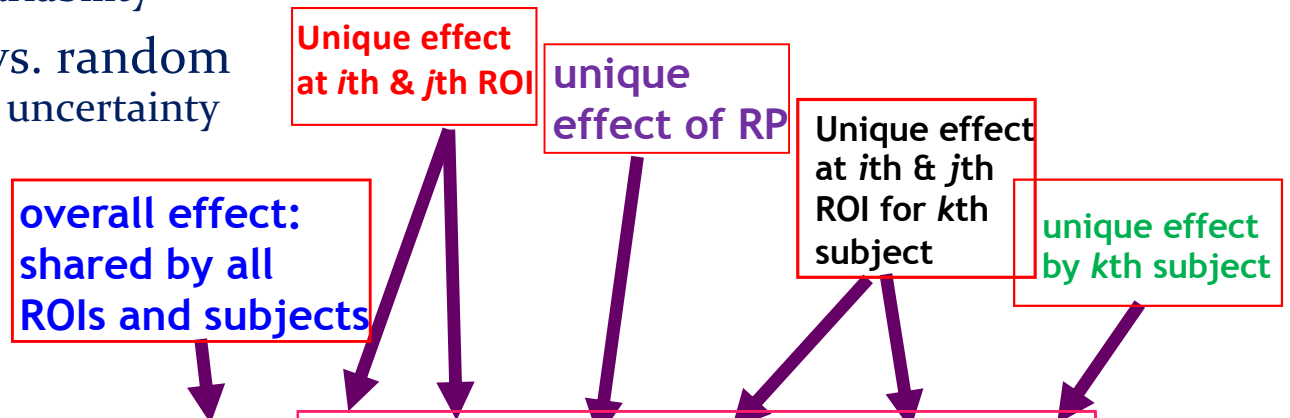
# IRC: switching from GLM to LME

- **IRC analysis through linear mixed-effects (LME) 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
  - Differentiation: fixed vs. random
    - Fixed: **epistemic** uncertainty
    - Random: **aleatoric** uncertainty
  - Effects of interest
    - region pair: $b_0+\xi_i+\xi_j+\eta_{jj}$
    - region: $0.5*b_0+\xi_i$
  - **LME wouldn't work!**
    ***Dead end!***



# IRC: one more jump from LME to BML

- **IRC analysis through Bayesian multilevel (BML) modeling**
  - One model integrates all ROIs: BML (essentially same as LME)
  - ROIs loosely constrained instead of being unrelated
    - Gaussian distribution: Is it far-fetched?
    - Similar to cross-subject variability
  - No differentiation: fixed vs. random
    - All parameters: **aleatoric** uncertainty
  - Effects of interest
    - region pair: $b_0+\xi_i+\xi_j+\eta_{jj}$
    - region: $0.5*b_0 + \xi_i$
  - LME plus priors
    - MCMC
    - Posterior distribution
  - ***Ka-ching!***

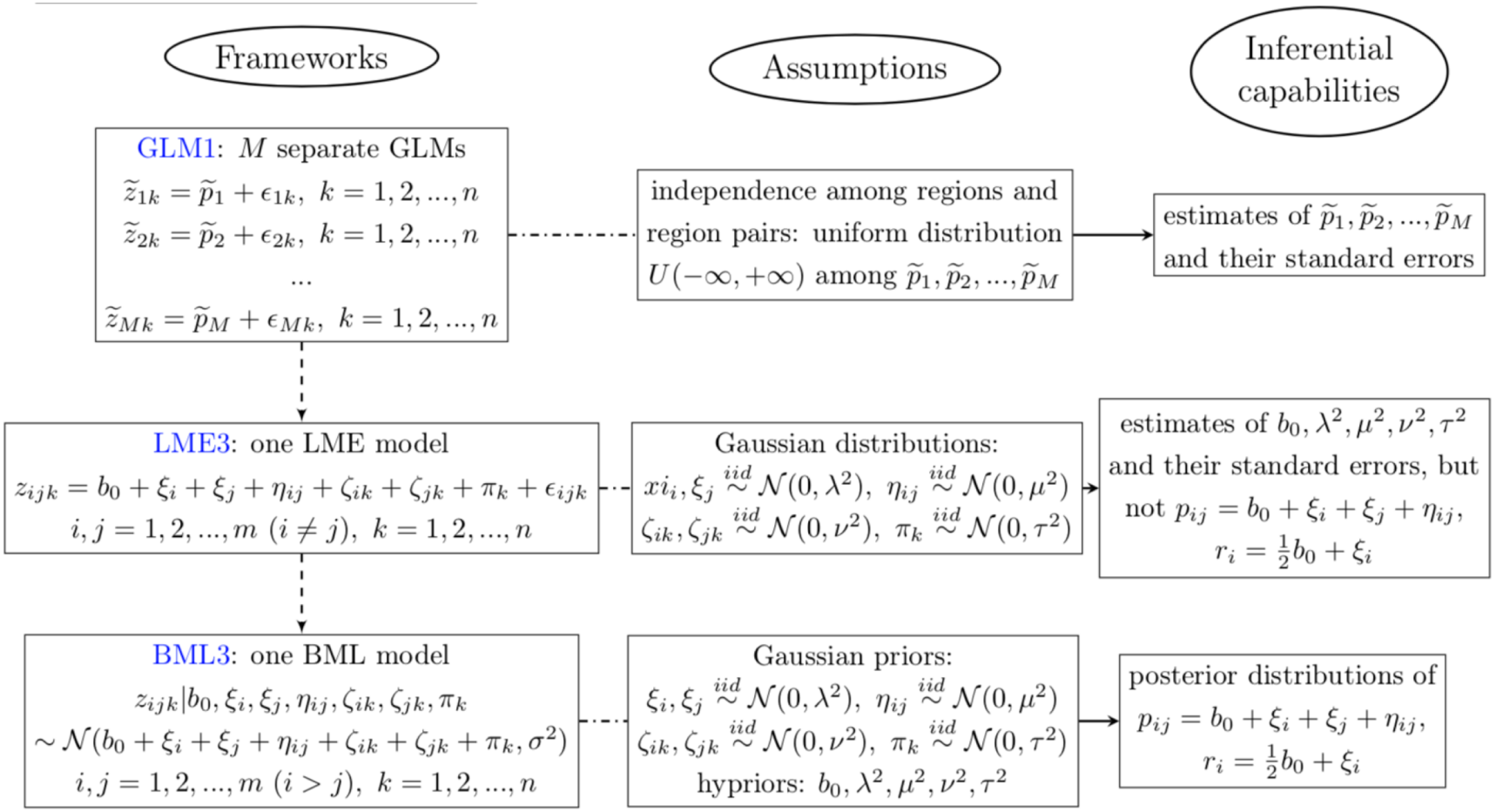



$$z_{ijk} = b_0 + \xi_i + \xi_j + \eta_{ij} + \zeta_{ik} + \zeta_{jk} + \pi_k + \epsilon_{ijk}$$

$$\xi_i, \xi_j \overset{iid}{\sim} \mathcal{N}(0, \lambda^2),\ \eta_{ij} \sim \mathcal{N}(0, \mu^2),\ \zeta_{ik}, \zeta_{jk} \sim \mathcal{N}(0, \nu^2),\ \pi_k \overset{iid}{\sim} \mathcal{N}(0, \tau^2),\ \epsilon_{ijk} \sim \mathcal{N}(0, \sigma^2)$$
$$i, j = 1, 2, ..., m\ (i > j),\ k = 1, 2, ..., n$$

Chen, et al, 2019. An integrative Bayesian approach to matix-based analysis in neuroimaging. bioRxiv.

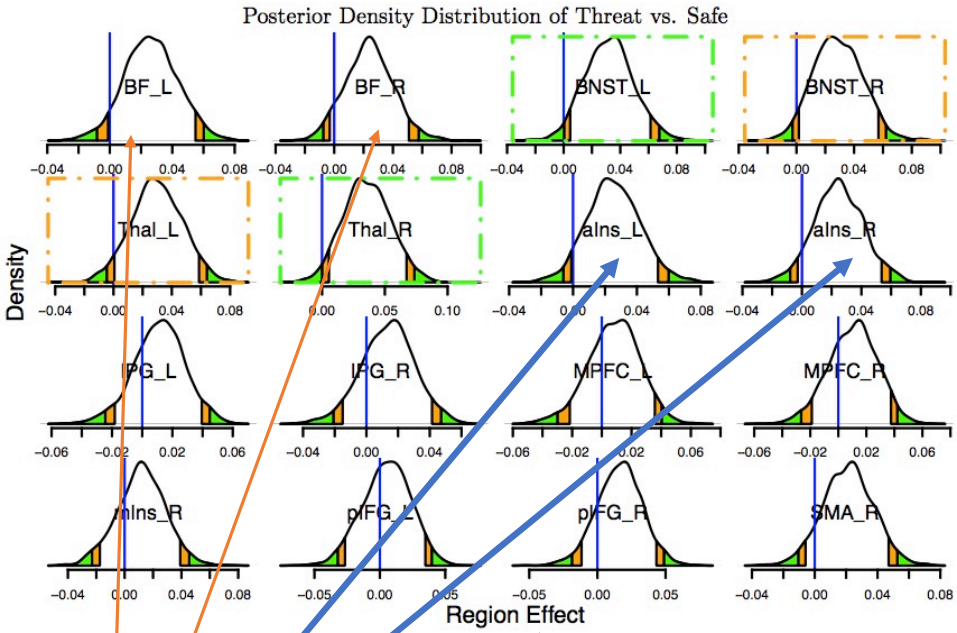
# From GLMs to LME to BML




Chen, et al, 2019. An integrative Bayesian approach to matix-based analysis in neuroimaging. bioRxiv.

# IRC – 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?



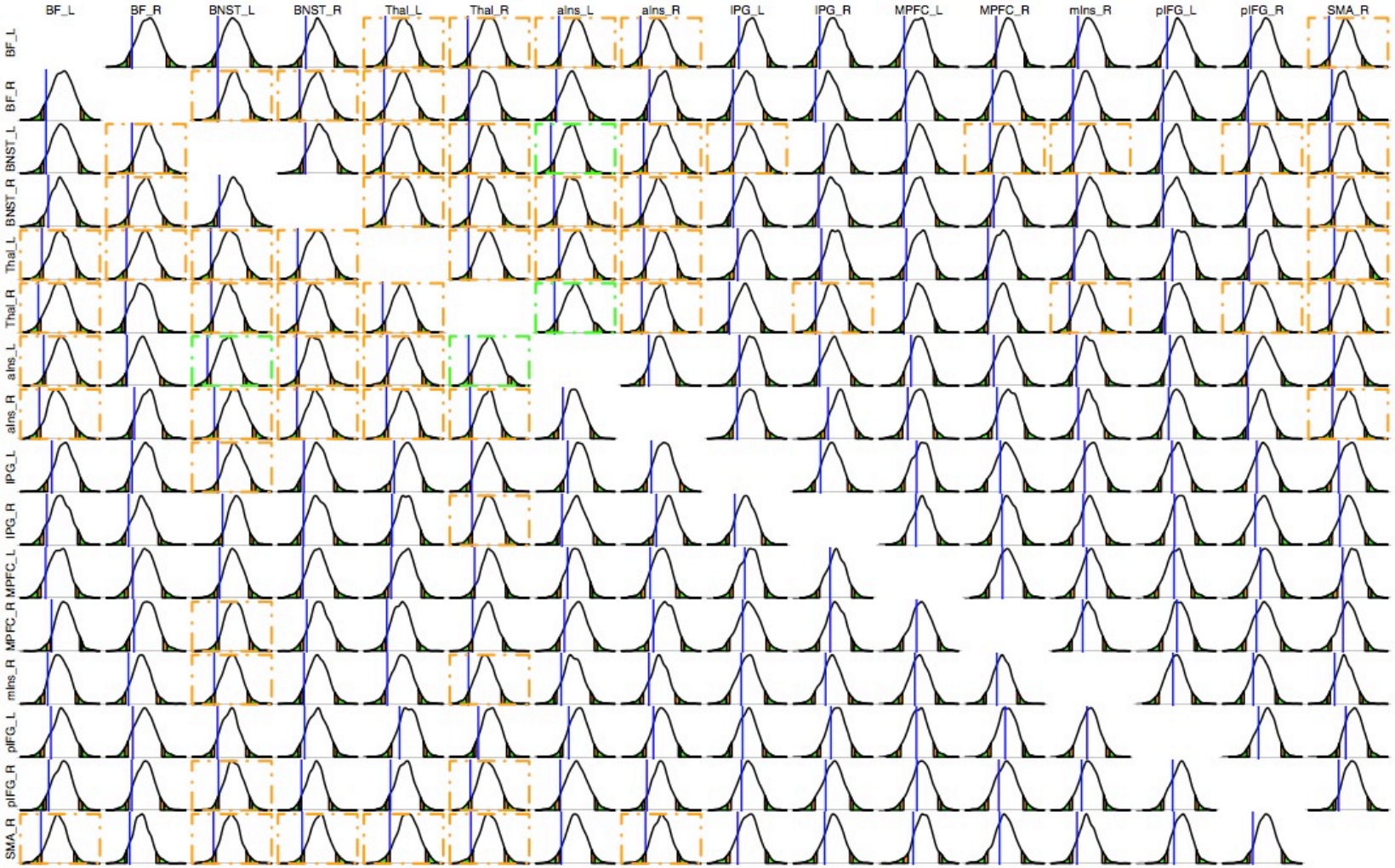

How about Left & Right Anterior Insula?

**Highlight, not hide**

# IRC – RP effect from BML: full distributions

120 RPs

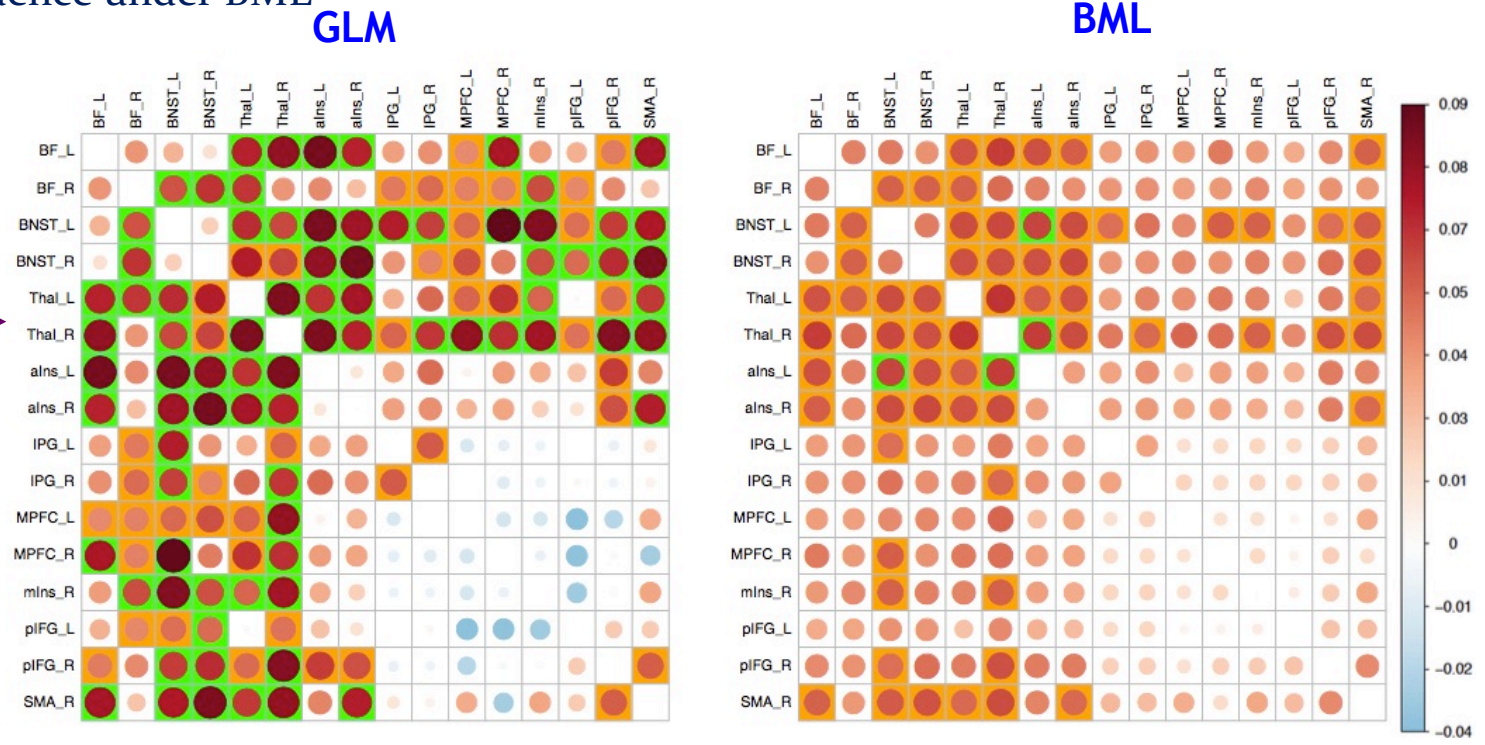
Highlight, not hide



# IRC– 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

Highlight, not hide



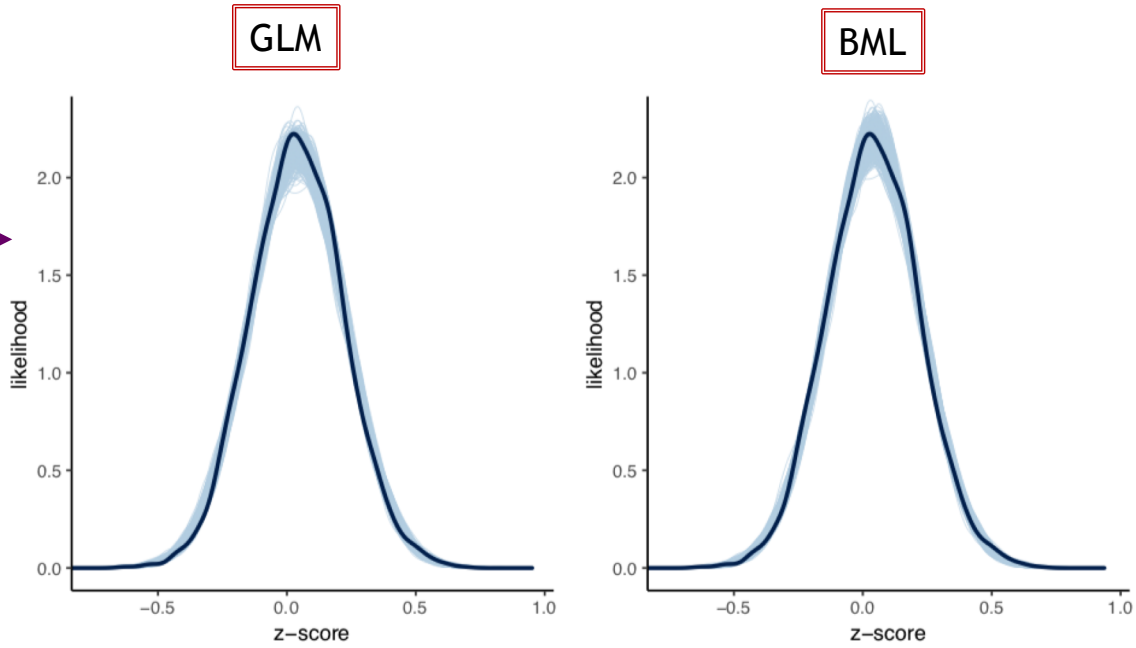
# BML: model validations

- **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

- **Multiplicity problems in neuroimaging**
- **Improved modeling from two perspectives**
  - Weirdness of *p*-value
  - Information waste and inefficient modeling
- **Application #1: region-based analysis (RBA)**
  - Task-related experiment or resting state (seed-based correlation analysis)

  Program available in AFNI: ***BayesianGroupAna.py***
- **Application #2: matrix-based analysis (MBA)**
  - FMRI: inter-region correlation (IRC)
  - DTI: white matter properties (FA, MD, etc.)
  - Naturalistic scanning: Inter-subject correlation (ISC)

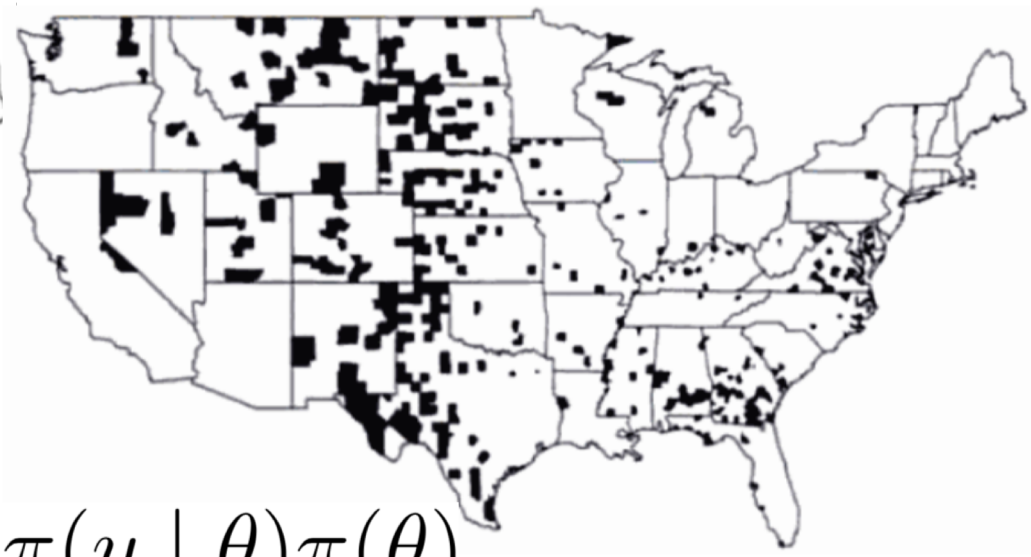
  Program available in AFNI: ***MBA***

# Keep Kidney Cancer in Mind!

- **Kidney cancer distribution among counties**

Highest rate

lowest rate



Calibration $\pi(\theta \mid y) = \dfrac{\pi(y \mid \theta)\pi(\theta)}{\pi(y)}$

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