

Advanced spatial Bayesian models for meta-analysis & reverse inference

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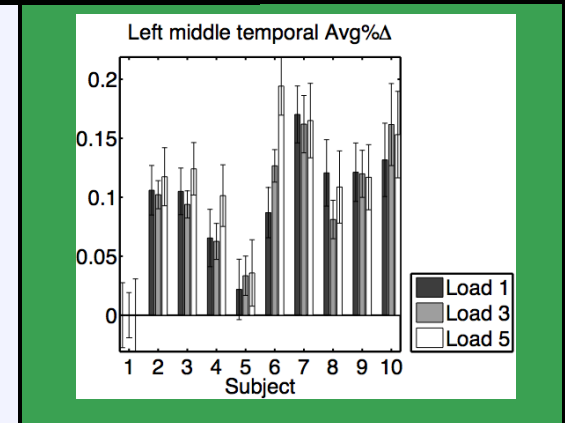
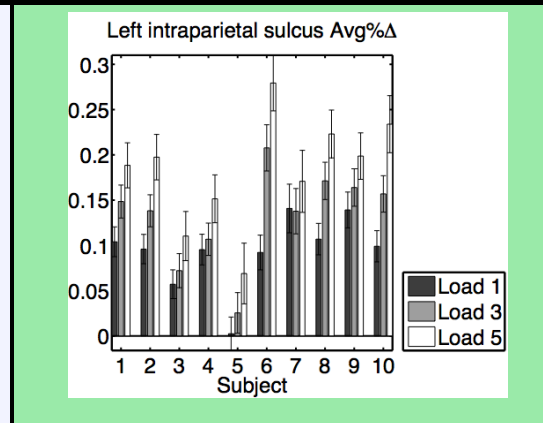
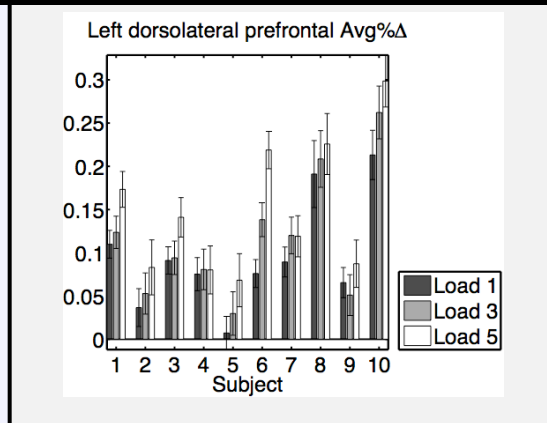
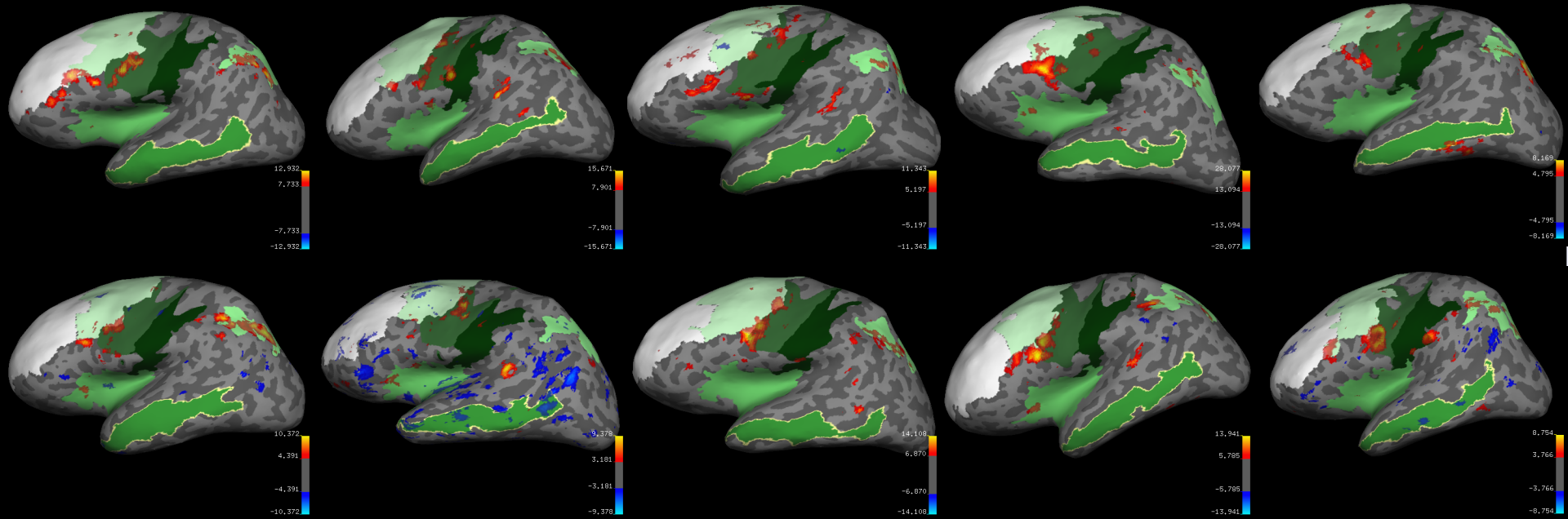
GSK – Neurophysics
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Overview

- Standard “Mass-univariate modelling”
 - Strengths & Limitations
- Bayesian Hierarchical Spatial Model
 - Group fMRI
 - Meta Analysis
 - Reverse Inference

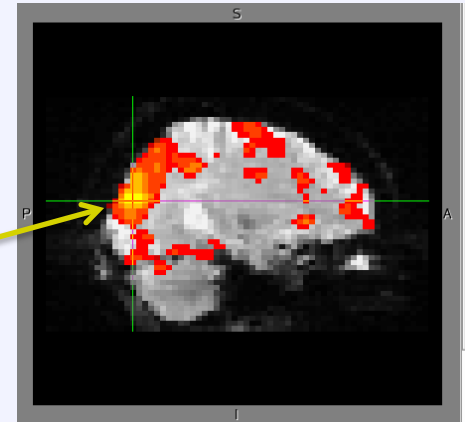
Huge Individual Variability

- 10 subjects, same fMRI working memory task
 - Profound variation in spatial location, ROI response

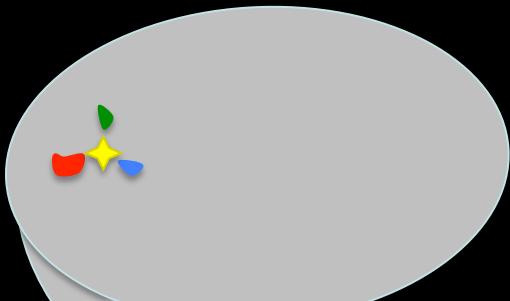


Mass-Univariate Can't Capture Spatial Heterogeneity

- Controls false positive risk
 - e.g. $T=5.56$, $p^{\text{FWE}} = 0.003$
 - But no inference on location
 - e.g. max T at $(40, -75, 10)$
but no confidence interval
 - “Result” is 100,000 Yes/No’s, significance at voxel
- Only see effects that co-align – thus smoothing



Individual responses
No smoothing



Toy Illustration:

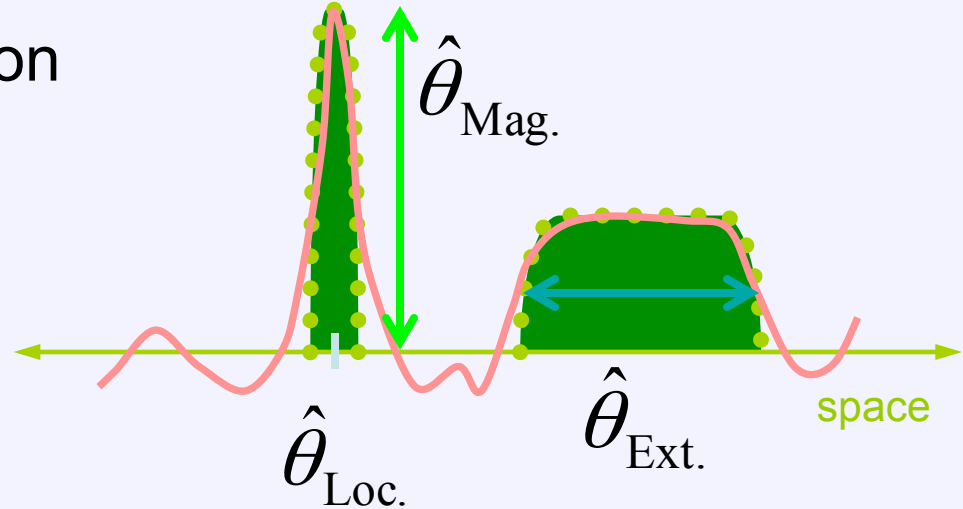
- 3 subjects' data before & after smoothing
- “Activation” only found where no one activates!

Individual responses
With smoothing



Blue-sky inference: What we'd like

- Don't threshold, **model the signal!**
 - Signal **location**?
 - Estimates and CI's on (x,y,z) location
 - Signal **magnitude**?
 - CI's on % change
 - Spatial **extent**?
 - Estimates and CI's on activation volume
 - Robust to choice of cluster definition



Real-life inference: What we get with mass-univariate

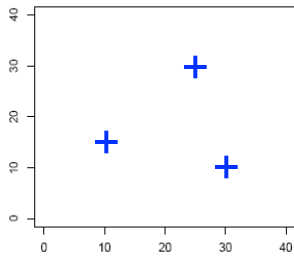
- Signal **location**
 - Local maximum – *no inference*
 - Center-of-mass – *no inference*
 - Sensitive to blob-defining-threshold
- Signal **magnitude**
 - Local maximum intensity – P-values (& CI's)
- Spatial **extent**
 - Cluster volume – P-value, no CI's
 - Sensitive to blob-defining-threshold
- Need explicit spatial modelling

Our Spatial Hierarchical Model

- Level 1: Population Centers
 - Center of activation in the population
- Level 2: Individual Centers
 - Center of local activation for a subject
 - Clustered about population centers
- Level 3: Individual Components
 - Capture shape of individual's activations
 - Clustered about individual centers
- Level 4: Observed fMRI Data
 - Mixture of a 'null' background Gaussian & non-null Gaussians, one per Individual Component

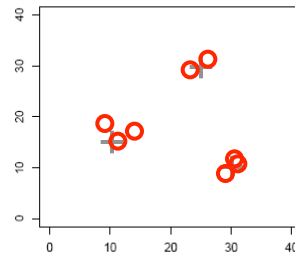
4-Level Spatial Hierarchy

“Population Centers”



Level 1:
Population
Activation
Location

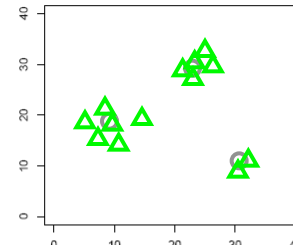
“Individual Centers”



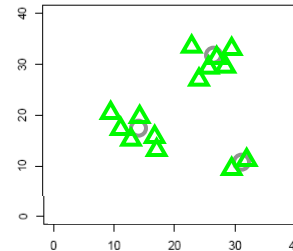
Level 2:
Individual
Activation
Location

- + Population Center
- o Individual Center
- △ Individual Component Center

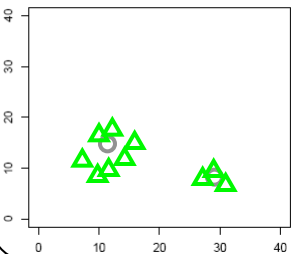
Subject 1



“Individual Components”

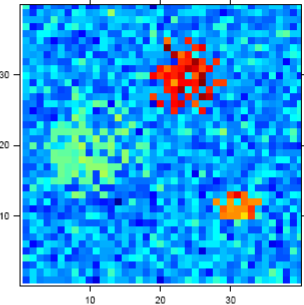


Subject 3

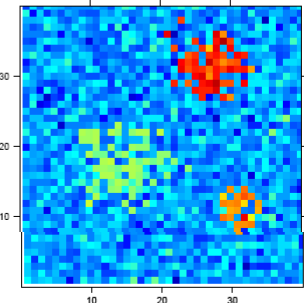


Level 3:
Individual
Activation
Shape

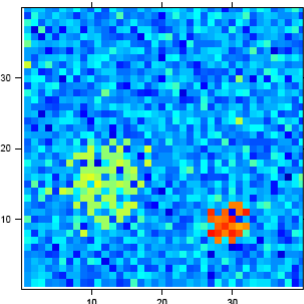
Subject 1



Subject 2



Subject 3



Level 4:
Individual
Data

Posterior Sampling

- Posterior complicated, but factorable
- Number of individual components, individual centers, population centers
 - Reversible Jump MCMC
 - $P_{\text{birth}} = P_{\text{death}} = 1/2$
 - Over-sample the RJ-MCMC moves 5× per iteration for better mixing
- Remaining parameters, conditional on # of centers
 - Gibbs or Metropolis-Hastings (MH)
 - Adaptive calibration of MH proposal variance to 35% acceptance rates

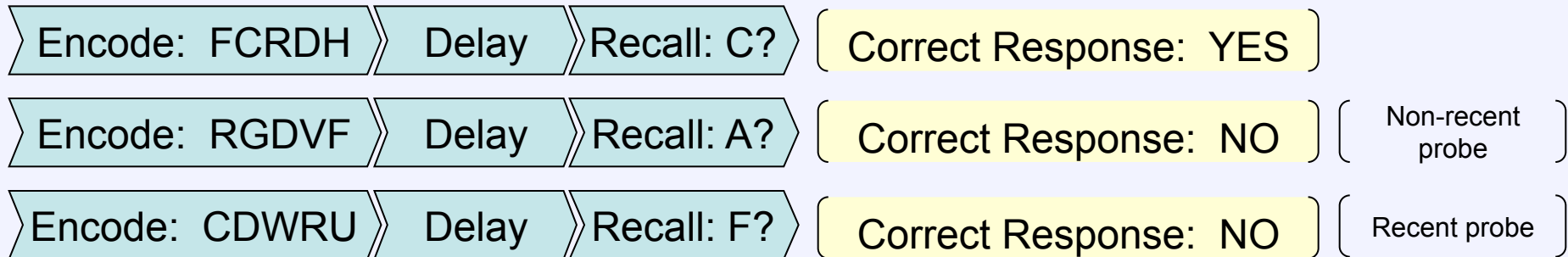
$$\begin{aligned}
 & \pi(\{\theta_{jl}\}, \{\eta_{jl}\}, \{\xi_{jh}\}, \{\mu_i\}, \{\varphi_{jh}\}, \{\psi_i\}, \{\sigma_{jl}^2\}, \{\Phi_{jh}\}, \{\mathbf{R}_{jl}\}, \{\Sigma_i\}, \{b_j\}, \{c_j\}, c_p, \mathbf{S}_\Sigma, \mathbf{S}_\Phi, \\
 & \quad \beta_\sigma, \lambda_\theta, \sigma_\theta^2 \mid \mathbf{y}) \\
 \propto & f(\mathbf{y} \mid \{\theta_{jl}\}, \{\eta_{jl}\}, \{\sigma_{jl}^2\}, \{\mathbf{R}_{jl}\}, \{c_j\}) \pi(\{\theta_{jl}\} \mid \{c_j\}) \times \\
 & \pi(\{\eta_{jl}\} \mid \{\varphi_{jh}\}, \{\xi_{jh}\}, \{\Phi_{jh}\}, \{c_j\}, \{b_j\}) \pi(\{\varphi_{jh}\} \mid \lambda_\varphi, b_j) \pi(\{\Phi_{jh}\} \mid \nu_\Phi, \mathbf{S}_\Phi, b_j) \times \\
 & \pi(\{\xi_{jh}\} \mid \{\psi_i\}, \{\mu_i\}, \{\Sigma_i\}, \{b_j\}, c_p) \pi(\{\psi_i\} \mid \lambda_\psi, c_p) \pi(\{\mu_i\} \mid c_p) \times \\
 & \pi(\{\sigma_{jl}^2\} \mid \beta_\sigma, \{c_j\}) \pi(\sigma_\theta^2 \mid \beta_{\sigma_\theta}) \pi(\{\Sigma_i\} \mid \nu_\Sigma, \mathbf{S}_\Sigma, c_p) \pi(\{\mathbf{R}_{jl}\} \mid \nu_r, \mathbf{T}_r, c_j) \times \\
 & \pi(\{c_j\}), \pi(\{b_j\}), \pi(c_p) \pi(\mathbf{S}_\Phi \mid f_\Phi, \mathbf{T}_\Phi) \pi(\mathbf{S}_\Sigma \mid f_\Sigma, \mathbf{T}_\Sigma) \pi(\beta_\sigma) \pi(\lambda_\theta) \pi(\sigma_\theta^2) \\
 = & \prod_{j=1}^J \prod_{v=1}^V \left(p_{jv0} (2\pi\sigma_0^2)^{-1/2} \exp[-0.5(y_{jv} - \theta_0)^2/\sigma_0^2] + \right. \\
 & \left. \sum_{l=1}^{c_j} p_{jvl} (2\pi\sigma_{jl}^2)^{-1/2} \exp[-0.5(y_{jv} - \theta_{jl})^2/\sigma_{jl}^2] \right) \times \\
 & (2\pi)^{-1/2} \exp(-0.5\theta_0^2) \prod_{j=1}^J \prod_{l=1}^{c_j} (2\pi\sigma_\theta^2)^{-1/2} \exp[-0.5(\theta_{jl} - \lambda_\theta)^2/\sigma_\theta^2] I(\theta_{jl} > 0) \times \\
 & \prod_{j=1}^J \prod_{l=1}^{c_j} \sum_{h=1}^{b_j} \varphi_{jh} (2\pi)^{-3/2} |\Phi_{jh}|^{-1/2} \exp[-0.5(\eta_{jl} - \xi_{jh})^T \Phi_{jh}^{-1} (\eta_{jl} - \xi_{jh})] \times \\
 & \prod_{j=1}^J \prod_{h=1}^{b_j} \prod_{i=1}^{c_p} \psi_i (2\pi)^{-3/2} |\Sigma_i|^{-1/2} \exp[-0.5(\xi_{jh} - \mu_i)^T \Sigma_i^{-1} (\xi_{jh} - \mu_i)] \times \\
 & \prod_{i=1}^{c_p} \left[2^{3\nu_\Sigma/2} \pi^{3/2} \prod_{k=1}^3 \Gamma\left(\frac{\nu_\Sigma + 1 - k}{2}\right) \right]^{-1} |\mathbf{S}_\Sigma^{-1}|^{\nu_\Sigma/2} |\Sigma_i|^{-(\nu_\Sigma+3+1)/2} \exp\left[-\frac{1}{2}\text{tr}(\mathbf{S}_\Sigma^{-1} \Sigma_i^{-1})\right] \times \\
 & \left[2^{3f_\Sigma/2} \pi^{3/2} \prod_{k=1}^3 \Gamma\left(\frac{f_\Sigma + 1 - k}{2}\right) \right]^{-1} |\mathbf{T}_\Sigma|^{f_\Sigma/2} |\mathbf{S}_\Sigma|^{-(f_\Sigma+3+1)/2} \exp\left[-\frac{1}{2}\text{tr}(\mathbf{T}_\Sigma \mathbf{S}_\Sigma^{-1})\right] \times \\
 & \prod_{j=1}^J \prod_{l=1}^{c_j} \left[2^{3\nu_r/2} \pi^{3/2} \prod_{k=1}^3 \Gamma\left(\frac{\nu_r + 1 - k}{2}\right) \right]^{-1} |\mathbf{T}_r^{-1}|^{\nu_r/2} |\mathbf{R}_{jl}|^{-(\nu_r+3+1)/2} \exp\left[-\frac{1}{2}\text{tr}(\mathbf{T}_r^{-1} \mathbf{R}_{jl}^{-1})\right] \times \\
 & \left[2^{3f_\Phi/2} \pi^{3/2} \prod_{k=1}^3 \Gamma\left(\frac{f_\Phi + 1 - k}{2}\right) \right]^{-1} |\mathbf{T}_\Phi|^{f_\Phi/2} |\mathbf{S}_\Phi|^{-(f_\Phi+3+1)/2} \exp\left[-\frac{1}{2}\text{tr}(\mathbf{T}_\Phi \mathbf{S}_\Phi^{-1})\right] \times \\
 & \prod_{i=1}^J \left[\frac{\Gamma(b_j \lambda_\varphi)}{\Gamma(\lambda_\varphi)^{b_j}} \prod_{h=1}^{b_j} \varphi_{jh}^{\lambda_\varphi - 1} \right] \frac{\Gamma(c_p \lambda_\psi)}{\Gamma(\lambda_\psi)^{c_p}} \prod_{i=1}^{c_p} \psi_i^{\lambda_\psi - 1} \prod_{i=1}^n \prod_{l=1}^{c_j} \left[\frac{\beta_\sigma^2}{\Gamma(2)} (\sigma_{jl}^2)^{-2-1} \exp(-\beta_\sigma/\sigma_{jl}^2) \right] \times
 \end{aligned}$$

Classical Comparison

- Mass univariate modelling
 - t-test image
 - $-\log_{10}$ P-value image
 - FWE & FDR thresholding

Real Data Application

- Pro-active Interference Resolution
 - Task consists of many trials, must remember letters on each trial only



- Must suppress memory of previous trials
- People are slower and less accurate when probe letter is from a recent (not current) trial
- fMRI contrast of selected trials
 - Correct “NO” response for recent probe *versus* Correct “NO” response for non-recent probe
 - Expected activation in lateral prefrontal cortex (LPFC)

Real Data Application

- *Unsmoothed* fMRI images from 18 subjects
 - Standardized to standard space, $79 \times 95 \times 69$ 2 mm³ voxels
- Mainly interested in left LPFC
 - Results focus on 1 slice, but model *is* fully 3D
- RJ-MCMC run for 2,000 burn-in plus 10,000 iterations
 - Acceptance rate for the population level birth/death RJMCMC $\approx 15\%$.
 - 8 hours of CPU time on MAC 3.0 GHz Xserve (21 hours for full 39-slice dataset)

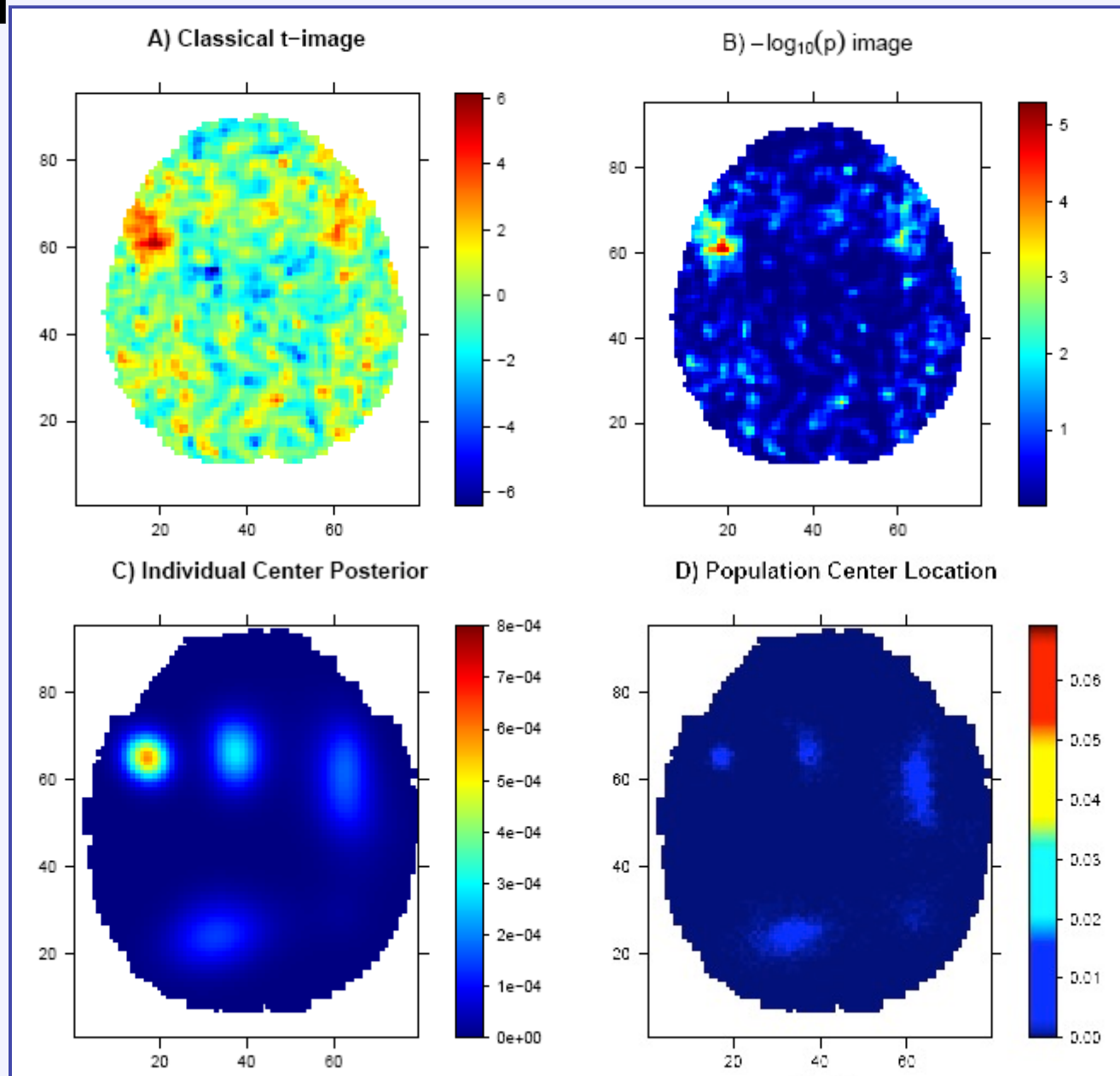
Hyperprior Parameter Settings

- Level 4: Observed data
 - $m = 19$, most optimistic prior prob. of null 0.95
 - $\lambda_c = 25$, prior mean # of individual components
- Level 3: Individual Component
 - $\lambda_b = 25$, prior mean # of individual centers
 - Small individual components
 - $T_\phi = (5/3)I$ gives a priori 95% spherical confidence region with radius 0.557 cm, volume 0.724 cm³ (the size of a Garbanzo bean).
- Level 2: Individual Centers
 - Larger spread of components about individual centers
 - $T_\Sigma = 5/(3 \times 2.5^2)I$ gives a priori 95% spherical confidence region with radius 1.392 cm, volume 11.31 cm³ (the size of a walnut).
- Level 1: Population Centers
 - λ_p set for a priori mean # of population centers of 5

Population Results

- Bayesian fit naturally 'de-noises'
- Much richer interpretation
 - Large intersubject spread
 - Precise information on population centers

Classical: No FWE or FDR 0.05 significance



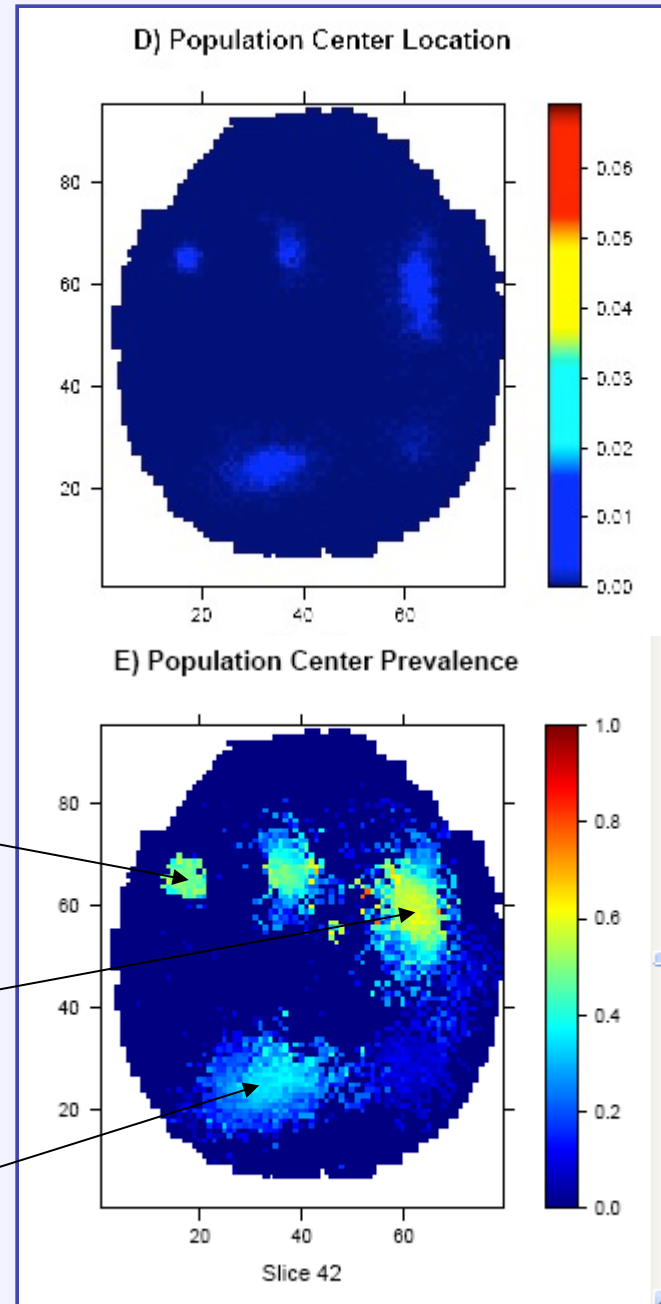
Population Result

- New insight into heterogeneity
 - “Population prevalence” of activation
 - At best, 60% of subjects studied had non-zero activation

≈ 50%

≈ 60%

≈ 35%

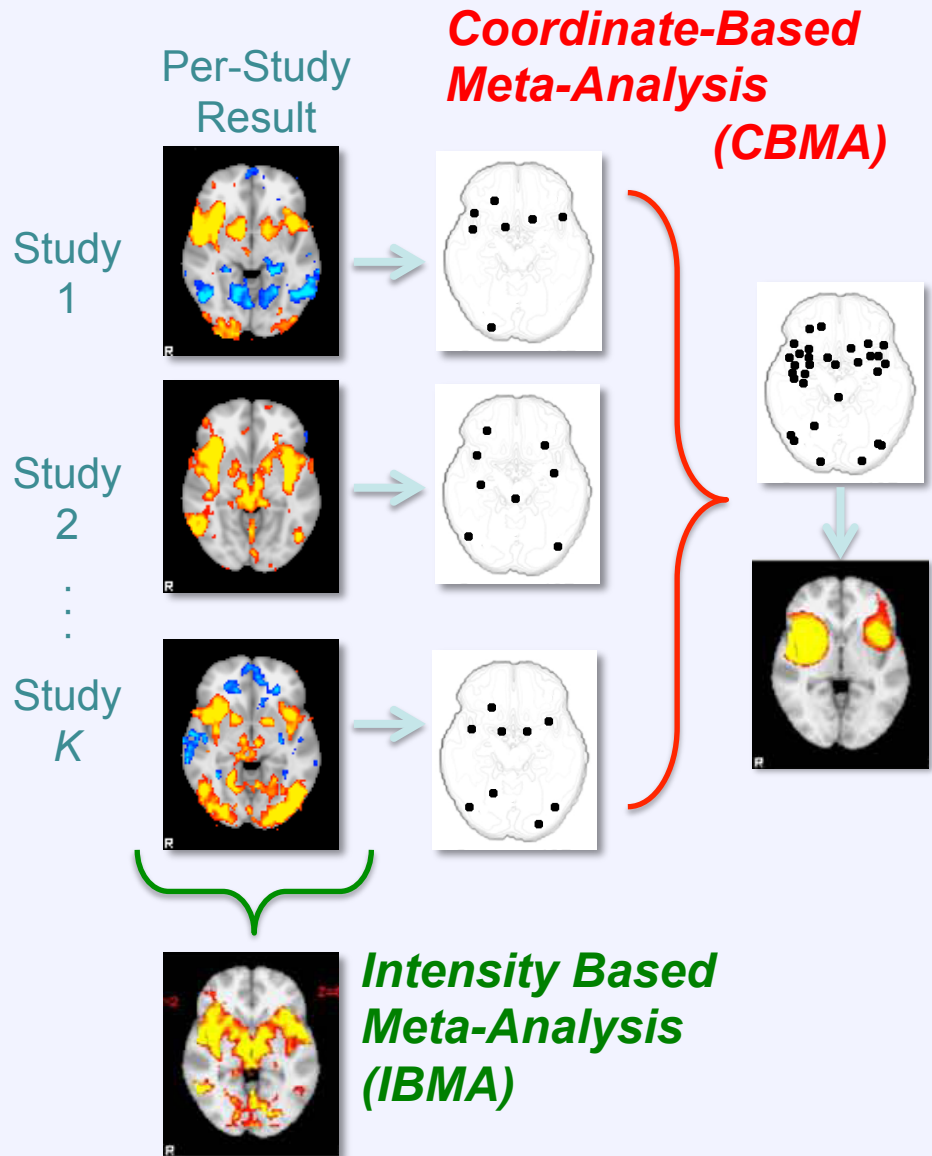


Conclusions: Group fMRI

- Group fMRI data exhibits incredible heterogeneity
- Mass univariate models only catch consistent ‘blurred together’ responses
- Explicit modelling of spatial structure
 - Provides rich interpretation of data
 - Remarkably precise localization of population centers
- Fully Bayesian model
 - Never turn-key, but worth the effort!

Meta-Analysis for Neuroimaging

- Now 20,000+ neuroimaging, including fMRI & PET studies
 - Tiny sample sizes e.g. median N of 13
 - Methodology heterogeneous
- Neuroimaging Meta-Analysis
 - Identify consistent results
 - Discount idiosyncratic findings
 - Explain inter-study variation



Methods for (non-imaging) Meta-Analysis (1)

- P-value (or Z-value) combining
 - Fishers (\approx average $-\log P$)
 - Stouffers (\approx average Z)
 - Used only as method of last resort
 - Based on significance, not effects in real units
 - Differing n will induce heterogeneity (Cummings, 2004)
- Fixed effects model
 - Requires effect estimates and standard errors
 - E.g. Mean survival (days), and standard error of mean
 - Gives weighted average of effects
 - Weights based on per-study standard errors
 - Neglects inter-study variation

Methods for (non-imaging) Meta-Analysis (2)

- Random effects model
 - Requires effect estimates and standard errors
 - Gives weighted average of effect
 - Weights based on per-study standard errors *and* inter-study variation
 - Accounts for inter-study variation
- Meta regression
 - Account for study-level regressors
 - E.g. year of publication, Impact Factor of journal, etc.
 - Fixed or random effects

Neuroimaging Meta-Analysis: Existing Approaches (1)

- Intensity-Based Meta-Analysis (IBMA)
 - With P/T/Z Images only
 - Only allows Fishers/Stouffers *Not best practice* 😞
 - With contrast/COPE's only
 - Only allows random-effects model without weights
 - Can't weight by sample size! *Not best practice* 😞
 - With COPE's & VARCOPES (contrasts & SE's)
 - FSL's FEAT/FLAME *is* the random effect meta model!
 - 2nd-level FLAME: Combining subjects
 - 3rd-level FLAME: Combining studies
 - “Mega-Analysis” regression *Best practice* 😊
 - But image data rarely shared *Bad practice* 😞

Neuroimaging Meta-Analysis: Existing Approaches (2)

- Coordinate-Based Meta-Analysis (CBMA)

- x,y,z locations only

- Activation Likelihood Estimation (ALE)

- **Turkeltaub et al. (2002)**. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *NeuroImage*, 16(3), 765–780.

- **Eickhoff et al. (2009)**. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping*, 30(9), 2907–26.

- **Eickhoff et al. (2012)**. Activation likelihood estimation meta-analysis revisited. *NeuroImage*, 59(3), 2349–61

- Multilevel Kernel Density Analysis (MKDA)

- **Wager et al. (2004)**. Neuroimaging studies of shifting attention: a meta-analysis. *NeuroImage* 22 (4), 1679–1693.

- **Kober et al. (2008)**. Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *NeuroImage*, 42(2), 998–1031.

- x,y,z and Z-value

- Signed Difference Mapping (SDM)

- **Radua & Mataix-Cols (2009)**. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry*, 195:391-400.

- **Costafreda et al. (2009)**. A parametric approach to voxel- based meta-analysis. *NeuroImage*, 46(1):115-122.

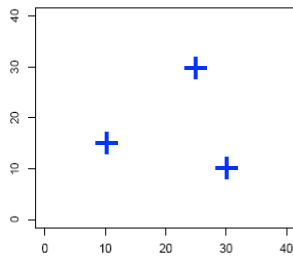
Bayesian Spatial Hierarchical Model

- CBMA still mass-univariate
 - Can't explicitly account for spatial structure
 - Only can detect spatially consistent effects
 - No (useful) information on different degrees of spread
 - Can't model the way users actually think about the data
 - True population location of effect
 - Individual subjects/studies fall with some spread
- Bayesian Marked Cox Clustering Process...
 - Joint with
 - Tim Johnson, Jiang Kang, University of Michigan Biostatistics
 - Tor Wager, Columbia University Psychology
 - Lisa Feldman Barrett, Northeastern University & MGH

Kang, Johnson, Nichols, Wager (2011). Meta Analysis of Functional Neuroimaging Data via Bayesian Spatial Point Processes. *J. Am. Stat. Assoc.* 106(493), 124-134.

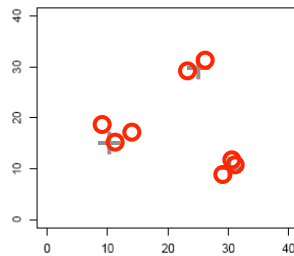
3-Level Spatial Hierarchy

“Population Centers”



Level 1:
Population Centres

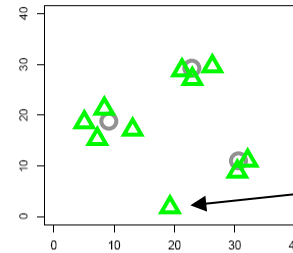
“Activation Centers”



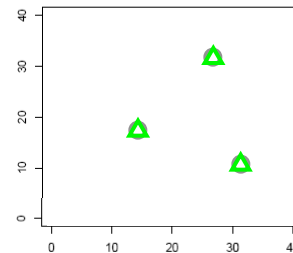
Level 2:
Study Activation Centres

- + Population Center
- o Study Center
- ▲ Study Foci Reported in paper

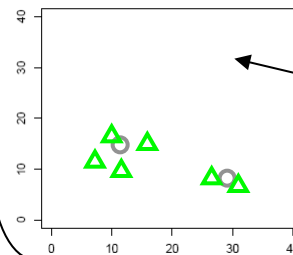
Subject 1



Subject 2



Subject 3



Level 3:
Study Foci

Features

Some foci may not “cluster”,
i.e. don’t belong to any centre

Some studies report only one focus per cluster; some multiple

Some studies may not have any foci from a population centre

Cox Cluster Process

- Poisson Process
 - $X \sim \text{Poisson}(\Omega, \lambda)$ for
 - Support $\Omega \subset \mathbb{R}^d$
 - Nonnegative rate function $\lambda: \Omega \mapsto [0, \infty)$
 - $X \in \Omega$ countable random variable
 - For any $S \subset \Omega$, $N_X(S)$ is Poisson random variable, rate
$$\mu(S) = \int_S \lambda(x) dx$$
- Cox Process
 - $X | \lambda \sim \text{Poisson}(\Omega, \lambda)$, random λ
- Cox Cluster Process
 - λ takes specific form of
 - $\lambda(\cdot | \mathbf{Y}) = \sum_{y \in \mathbf{Y}} f(\cdot | y)$
 - e.g. $\mathbf{Y} = \{ (x_1, y_1, z_1), (x_2, y_2, z_2), \dots, \}$
location of latent activation centres

Cox Cluster Process with Marks

- Population Centres

- Marked latent process
- Each y has mark, a 3×3 matrix Σ of inter-study spread

$$\lambda(\cdot | \mathbf{Y}) = \varepsilon + \sum_{y \in \mathbf{Y}} f(\cdot | y)$$

- Study Centres

- Location about which come observed foci
- *If* multiple foci in neighbourhood, model “intra-study” spread
 - If only one focus per apparent population center, then not

- Background intensity

- “Noise”, loci that don’t cluster (rate ε)

- Fully Bayesian model

- Posterior simulation with Spatial Birth-and-Death Algorithm (van Lieshout and Baddeley, 2002)

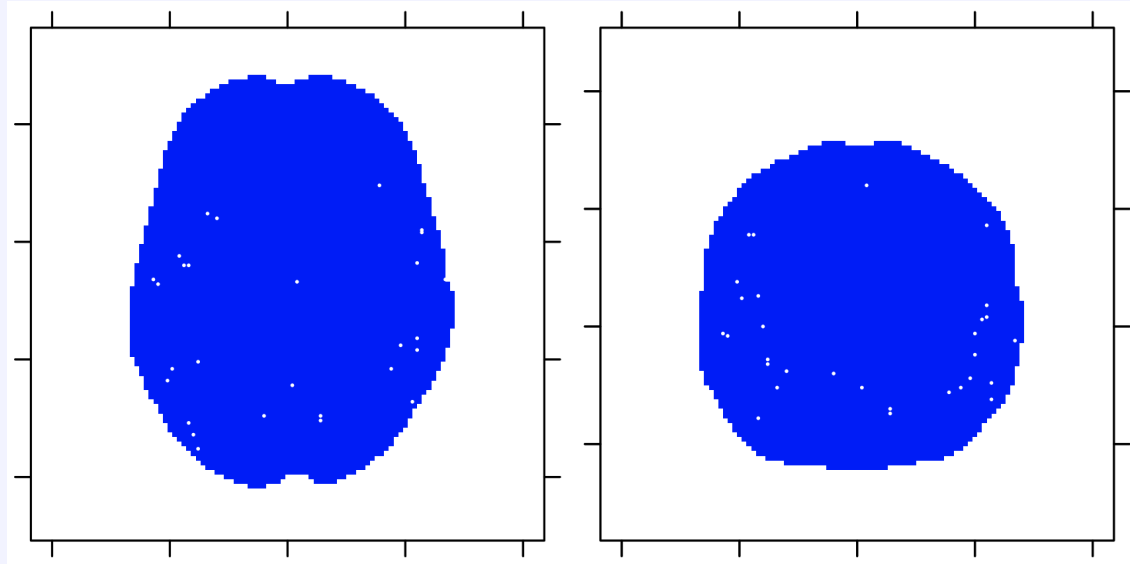
Example of CBMA Data

- Neuroimaging Studies of Emotion
 - 164 studies
 - Avg. n is 12 ($4 \leq n \leq 40$)
 - 2350 peaks in total
 - Emotions studied: sad, happy, angry, fear, disgust, surprise, affective and mixed
- Goal
 - Find regions of consistent emotion-induced activations

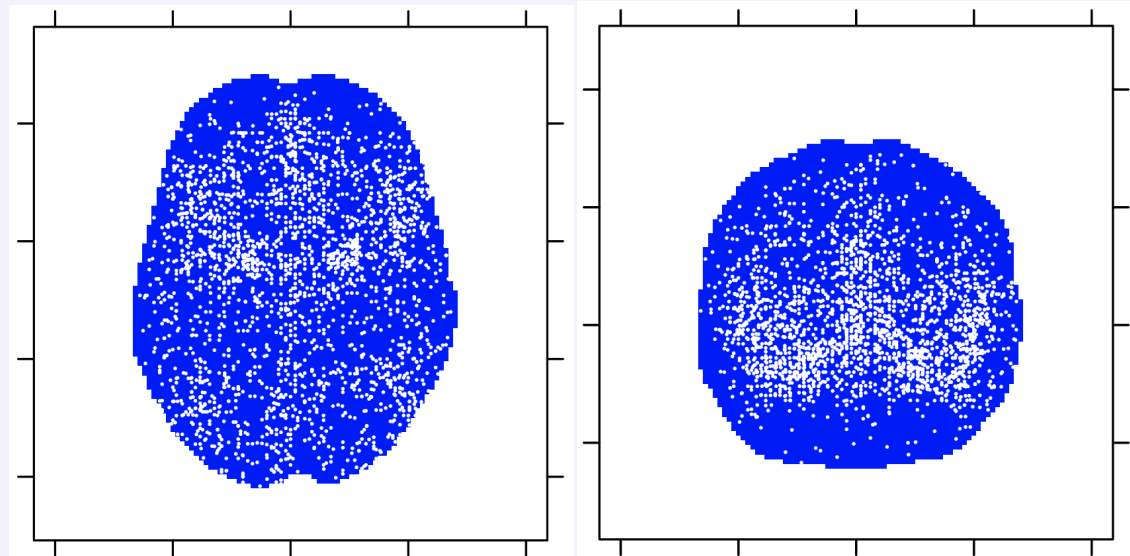
Example of CBMA Data

- x,y,z coord. in MNI (standard atlas) space)
- Each study has multiple points

Foci from 1 study



Foci from all 164 studies



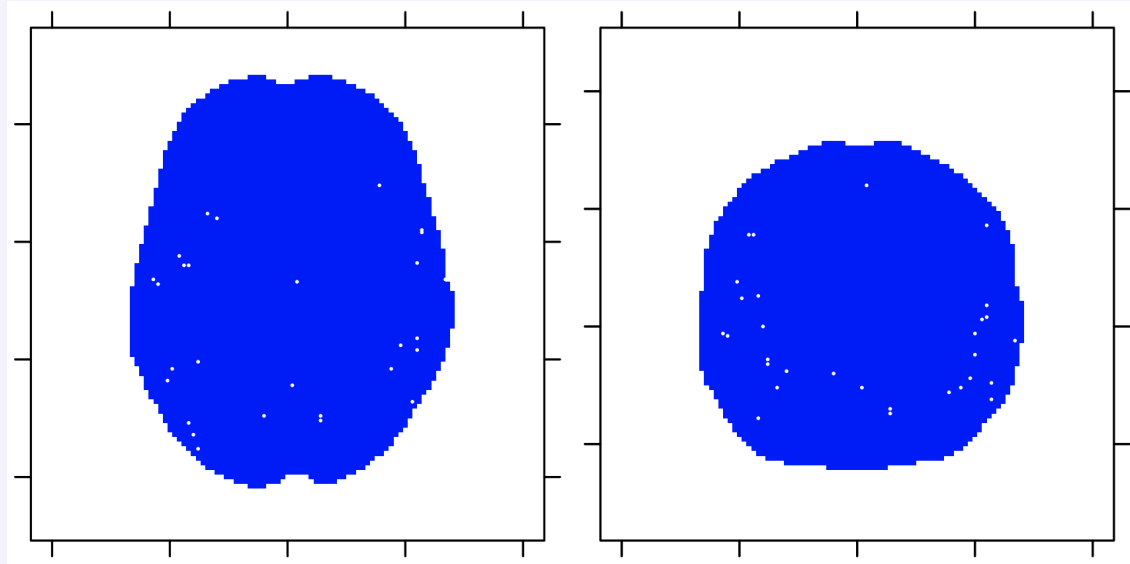
Axial View
(from atop head)

Coronal View
(from behind head)

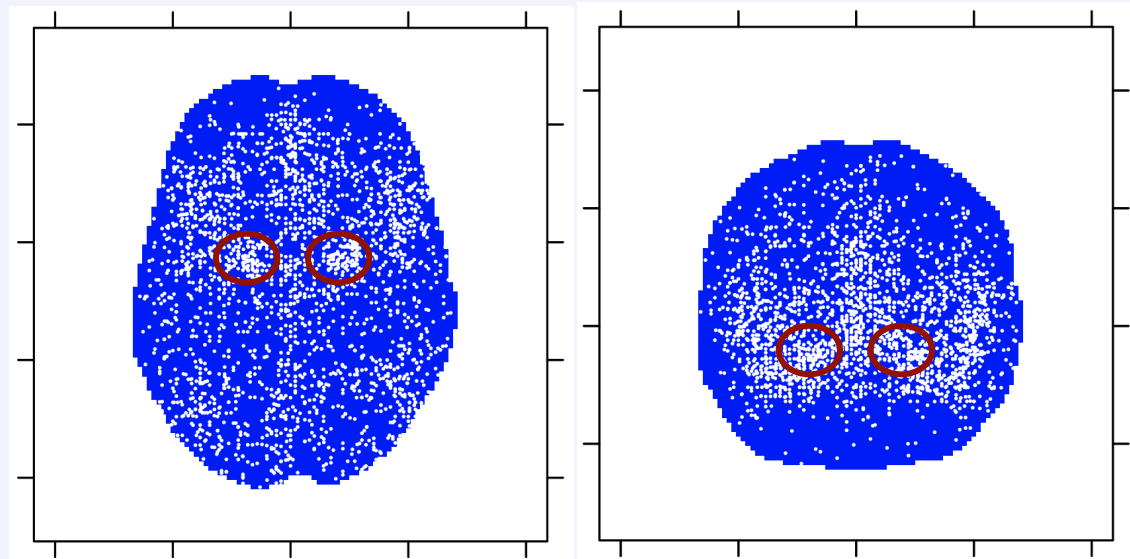
Example of CBMA Data

- x,y,z coord. in MNI (standard atlas) space)
- Each study has multiple points
- We focus on **amygdala**

Foci from 1 study



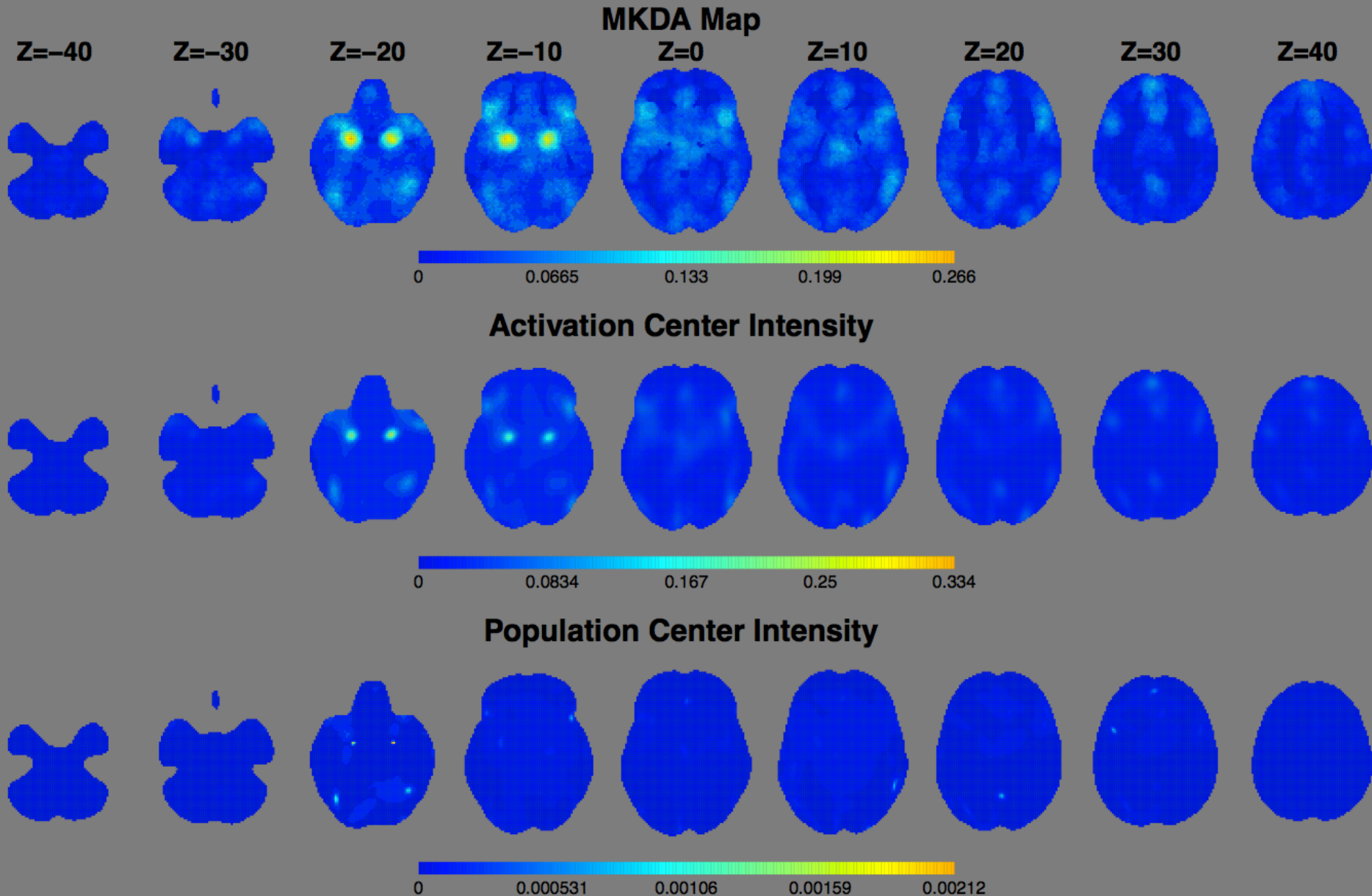
Foci from all 164 studies



Axial View
(from atop head)

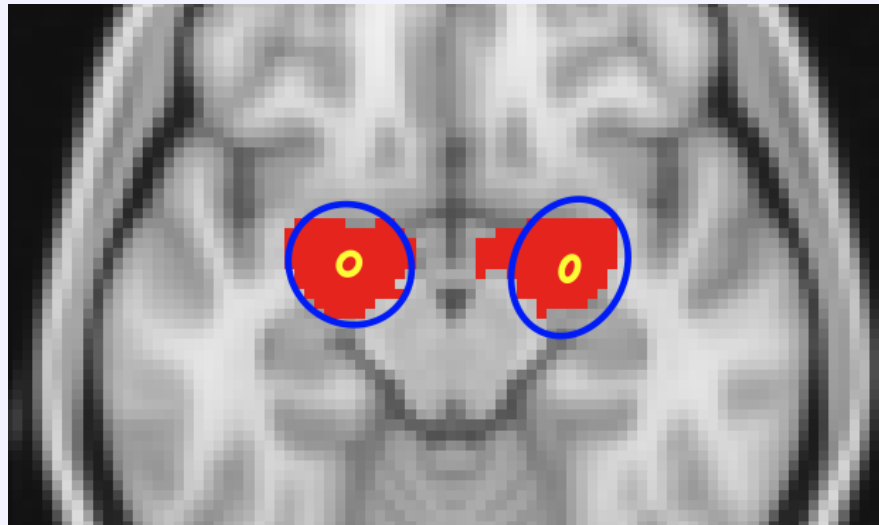
Coronal View
(from behind head)

Posterior Fit & Comparison



Posterior Fit

- 95% credible ellipses
 - Study-level centres (blue)
 - Population centres (yellow)
 - Amygdala voxels shown in red (Harvard-Oxford atlas)



Allows clear distinction between
Estimation of inter-study spread of loci, and
Inference on location of population centre

Meta-Analysis Study Classification

- Fit Bayesian model separately 5 times

	Sad	Happy	Anger	Fear	Disgust
Studies	45	36	26	68	44
Foci	346	177	166	367	337

- Note, data very sparse

Foci per Study	7.7	4.9	6.4	5.4	7.7
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- This is a challenge, but
 - Total counts informative of study type
- Can then predict one new (held-out) study

LOOCV Classification Accuracy

- Our model
 - 83% avg.
 - 69% worst
- GNB with MKDA
 - 45% avg.
 - 0% worst
- Accurate model

Bayesian Spatial Point Process Model (0.83)

Truth	Prediction				
	sad	happy	anger	fear	disgust
sad	0.78	0.00	0.11	0.04	0.07
happy	0.06	0.92	0.00	0.03	0.00
anger	0.08	0.08	0.69	0.15	0.00
fear	0.13	0.01	0.00	0.85	0.00
disgust	0.05	0.02	0.02	0.07	0.84

MKDA based Naive Bayes Classifier (0.45)

Truth	Prediction				
	sad	happy	anger	fear	disgust
sad	0.38	0.11	0.07	0.40	0.04
happy	0.11	0.25	0.03	0.56	0.06
anger	0.12	0.23	0.00	0.50	0.15
fear	0.06	0.06	0.01	0.81	0.06
disgust	0.09	0.16	0.05	0.32	0.39

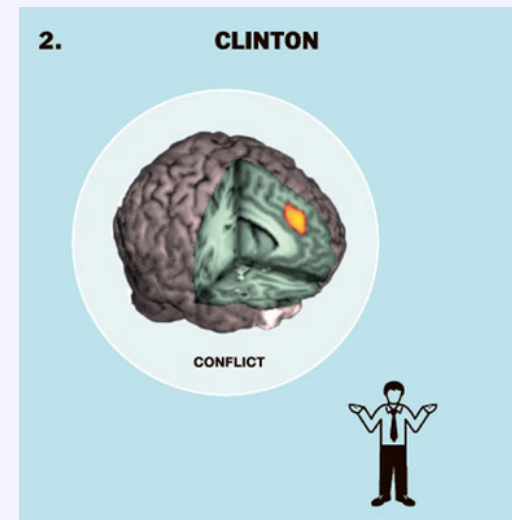
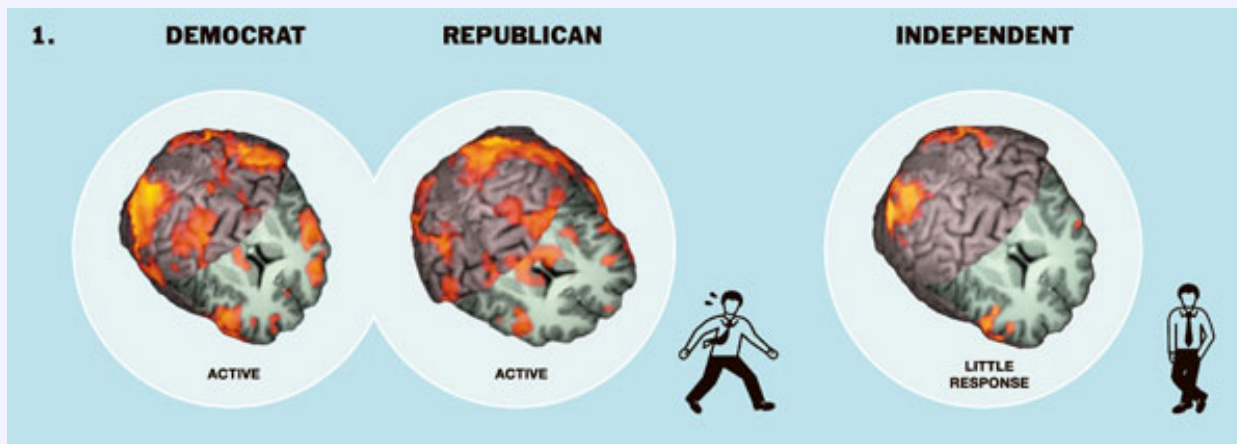
Chance Accuracy = $1/5 = 0.20$

Conclusions: Meta Analysis

- Intensity-Based *Mega* Analysis (IBMA)
 - Always preferred to use the original data
- CBMA with ALE/(M)KDA, etc
 - Suffers from all limits of mass-univariate modelling
- CBMA & detailed spatial hierarchical model
 - Much more interpretable model

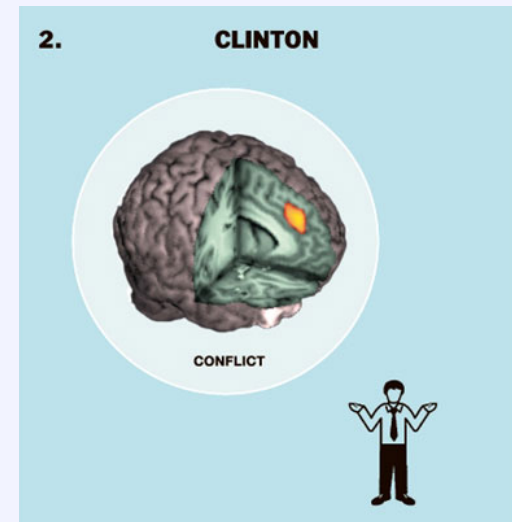
Reverse Inference & Brain Imaging

- Politics study
 - N=20 voters viewing images of candidates
 - Voters who, a priori, disliked Hillary Clinton, “exhibited significant activity in the anterior cingulate cortex, an emotional center” ..., activated when one “feels compelled to act in two different ways but must choose one.”



Reverse Inference & Brain Imaging

- Logic
 - Emotion conflict resolution task
 - Anterior Cingulate activation
 - Hillary Clinton
 - Anterior Cingulate
 - Ergo
 - Hillary Clinton induces emotional conflict



→ Faulty Reverse Inference

- High $P(\text{A.C. Act.} \mid \text{Emot. Conf.})$ *doesn't imply* high $P(\text{Emot. Conf.} \mid \text{A.C. Act.})$!!!

Reverse Inference & Brain Imaging

- Bayes Rule

- $$P(E=e|A) = \frac{P(A|E=e) P(E=e)}{\sum_{e^*} P(A|E=e^*)P(E=e^*)}$$

- Must sum over all possible “e*”, all different possible types of experiments

- Can we find “P(Emot. Conf. | A.C. Act.)”?

- Would have to run 100’s of experiments!

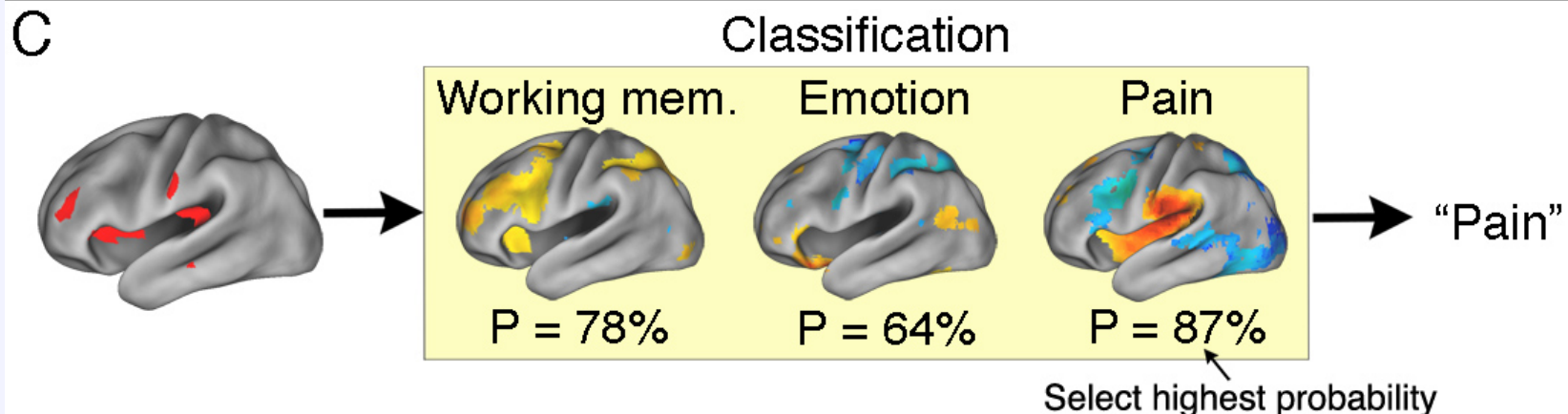
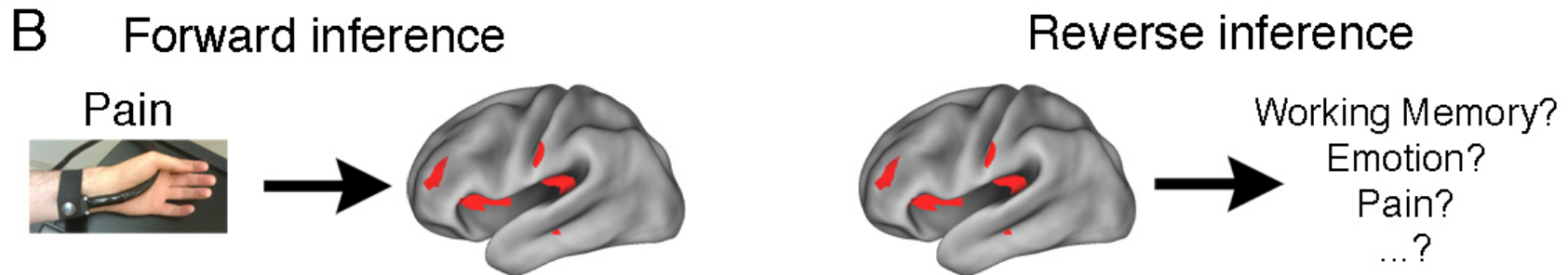
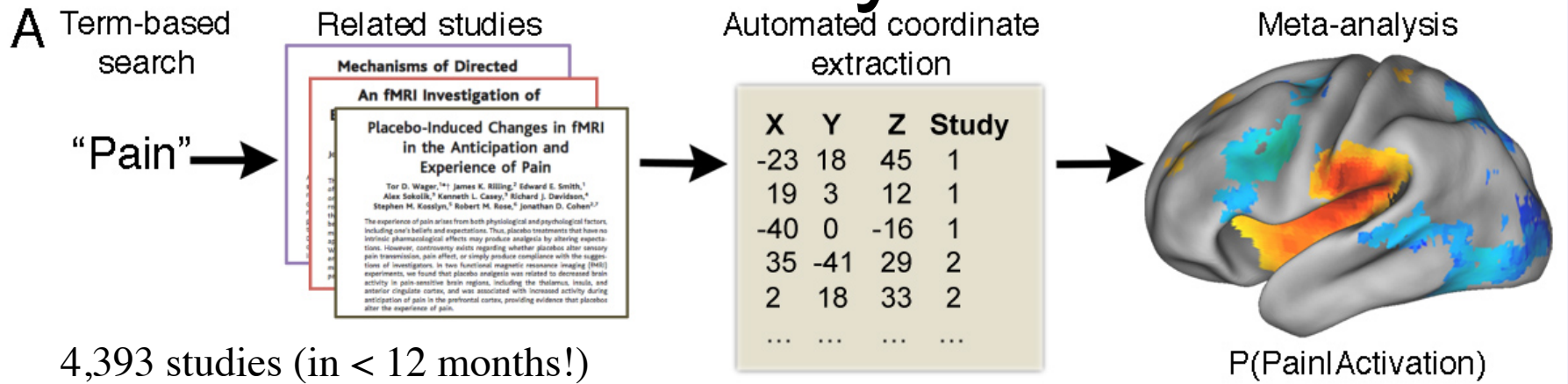
- Or, use meta analysis!

- But best Neuroimaging Meta Analysis databases are still limited

- BrainMap.org has 2155 studies (first in 1988)

- Pubmed finds 288,850 refs with “fMRI”

Neurosynth

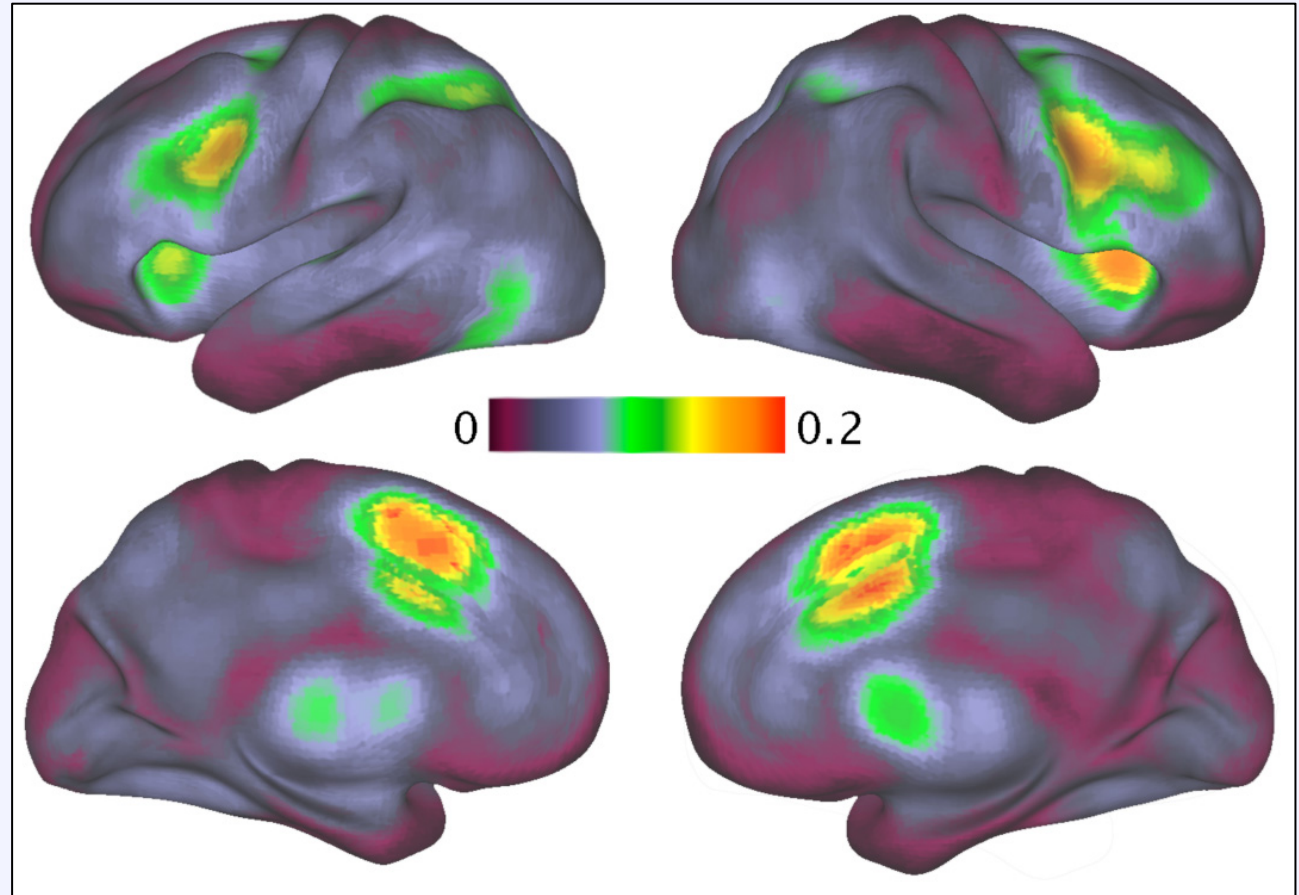


Yarkoni, Poldrack, Nichols, Essen, & Wager (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, 8(8), 665-670. www.neurosynth.org

What about Anterior Cingulate?

- It's always there!

Probability of activation over all studies



- Finally, can do real reverse inference...

Previous meta-analyses

Automated meta-analysis

A

B

C

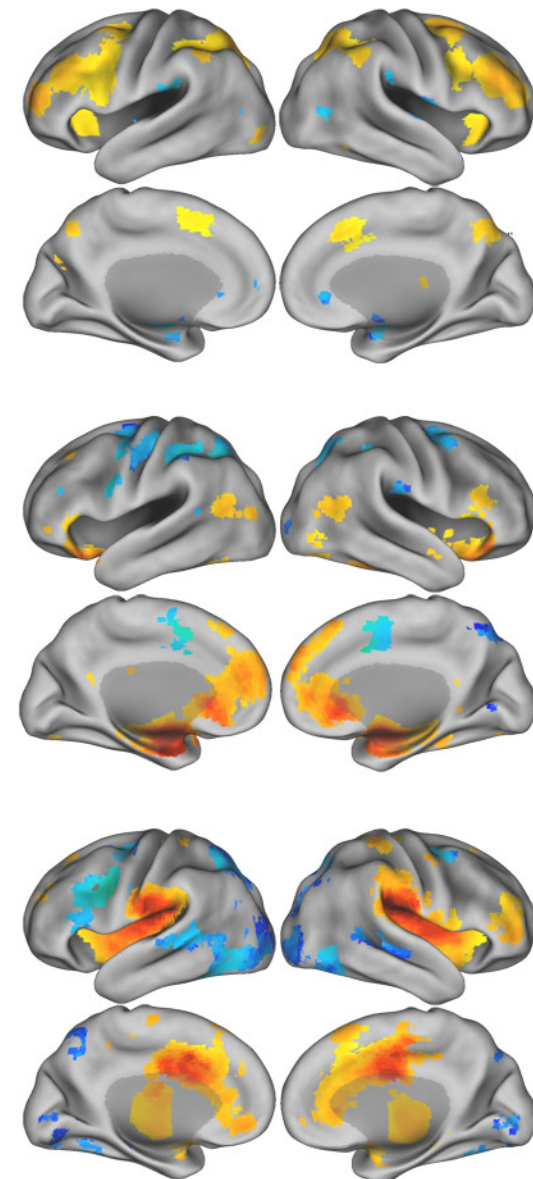
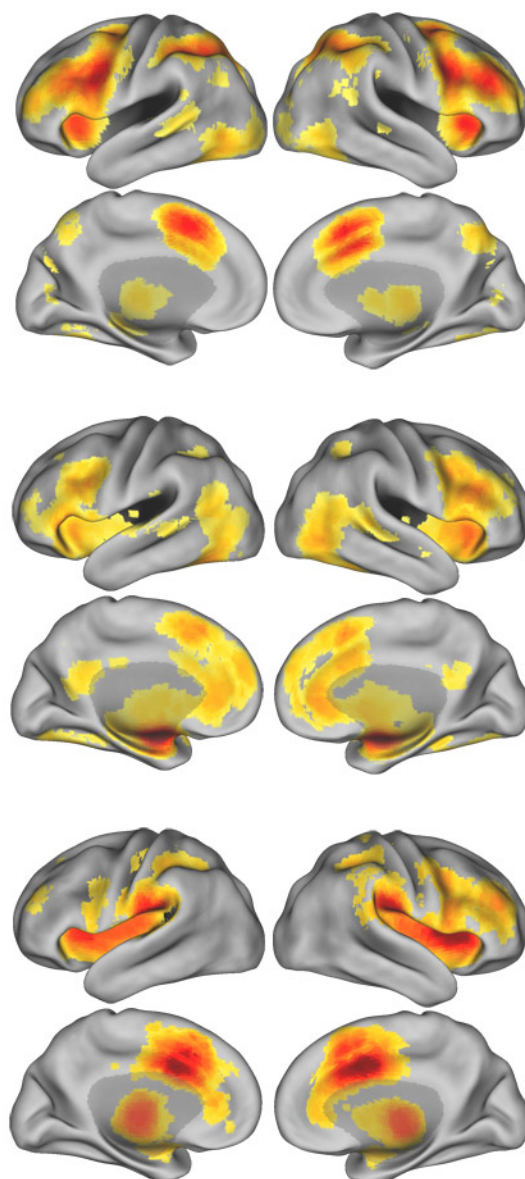
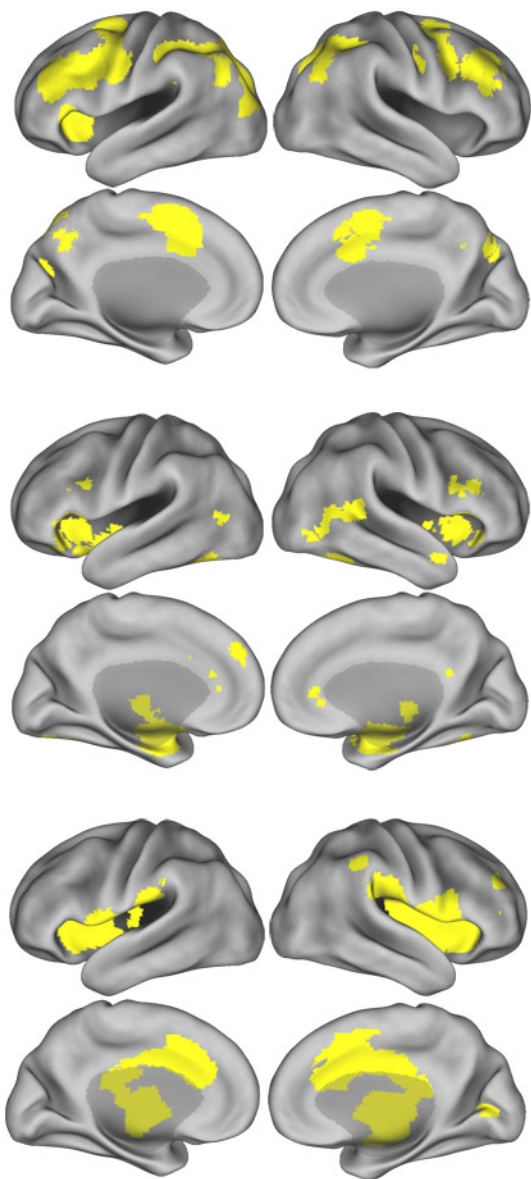
Forward Inference
($P(\text{Act}|\text{Term})$)

Reverse Inference
($P(\text{Term}|\text{Act})$)

Working
Memory

Emotion

Pain



0 $P(\text{Act}|\text{Term})$ 0.4

0.1 $P(\text{Term}|\text{Act})$ 0.9



Final Conclusions

- Accurate Spatial Modelling
 - Provide more interpretable models
 - Better predictive performance
- Bayesian Spatial Models
 - Not turn-key
 - Answers questions mass univariate can't

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- Group fMRI Spatial Modelling
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Thank you!